Maria Vuorilehto

Depressive Disorders in Primary Health Care

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Department of Mental Health and Alcohol Research
National Public Health Institute
and
Department of Psychiatry
University of Helsinki

Helsinki, Finland 2008

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Helsinki, Finland
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Department of Psychiatry,
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Maria Vuorilehto

DEPRESSIVE DISORDERS IN PRIMARY HEALTH CARE

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine, Institute of Clinical Medicine, Department of Psychiatry, University of Helsinki, for public examination at the Christian Sibelius-auditorium, Välskärinkatu 12, on May 16th, at 12 noon.

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Kansanterveyslaitos (KTL)
Mannerheimintie 166
FIN-00300 Helsinki, Finland
puh. (09) 4744 1, fax (09) 4744 08

Folkhälsoinstitutet
Mannerheimvägen 166
FIN-00300 Helsingfors, Finland
tel. (09) 4744 1, fax (09) 4744 08

National Public Health Institute (NPHI)
Mannerheimintie 166
FIN-00300 Helsinki, Finland
tel. +358-9-4744 1, fax +358-9-4744 08

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Supervised by

Professor Erkki Isometsä, M.D., Ph.D.
Department of Psychiatry, University of Helsinki, Finland
Department of Mental Health and Alcohol Research,
National Public Health Institute, Helsinki, Finland

Reviewed by

Professor Kaisu Pitkälä, M.D., Ph.D.
Department of General Practice and Primary Health Care,
University of Helsinki, Finland

and

Professor Heimo Viinamäki, M.D., Ph.D.
Department of Psychiatry, University of Kuopio, Finland

Opponent

Professor Raimo K.R. Salokangas, M.D., Ph.D.
Department of Psychiatry, University of Turku, Finland

Sänkyn kans

Tätä mää epäli. Mun sänk o masentunu.
Hän makka kaikep päivä pujamas ja huaaakaile vaan kova ääne.
Mää oti Mee naiste testi ja kyseli:

1.	*Onk paha miäl?*	*O.*
2.	*Eik mikkä huvit?*	*Ei.*
3.	*Väsyttäk?*	*Nimpaljessuksest.*
4.	*Tulek uni?*	*Ei millä.*
5.	*Paruttak?*	*Valla.*
6.	*Nauruttak?*	*Mikkä.*
7.	*Ark kaattu pääl?*	*Ko sein.*
8.	*Onk vaikkia?*	*Voi voi senttä.*
9.	*Misä unelma ova?*	*Hevom persses.*
10.	*Es sunkka sää ittiäs tappa meina?*	*Onk sänkyjaloil kiivet parvekken kaitte yli?*

An mää auta.

(Heli Laaksonen, Pulu uis 2000)

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TIIVISTELMÄ

Vantaan terveyskeskuksen masennustutkimus (PC-VDS) on perusterveydenhuollon (PTH) masennuspotilaiden etenevä seurantatutkimus ja osa Kansanterveyslaitoksen mielenterveys- ja alkoholitutkimusyksikön ja Vantaan sosiaali- ja terveystoimen yhteistyöhanketta. PC-VDS:n tarkoituksena on luoda aiempaa kattavampi käsitys PTH:n potilaiden depressiosta sekä verrata vakavaan masennustilaan liittyviä eroja ja yhteneväisyyksiä PTH:n ja psykiatrisen erikoissairaanhoidon potilaiden välillä.

Kolmen vantaalaisen terveysaseman 1111 satunnaista potilasta täyttivät Prime-MD – kyselyn. Heistä niitä, jotka kyselyssä ilmaisivat masennusoireita, haastateltiin vielä puhelimitse. Diagnostiseen haastatteluun (DSM-Axis I Disorders, SCID-I/P) kutsuttiin ne, joilla oli vähintään kaksi viikkoa jatkunut masentunut mieliala tai kiinnostuksen tai mielihyvän menetys. Lopullisen tutkimuskohortin muodostivat ne 137 potilasta, joilla oli masennustilan diagnostisista oireista vähintään kaksi sekä niiden aiheuttamaa kärsimystä tai toimintakyvyn heikkenemistä.

Tutkimuspotilailta kerättiin sekä poikkileikkauksellisia että takautuvia tietoja henkilökohtaisella haastattelulla ja kyselykaavakkeilla, lisäksi käytössä oli kaikki mahdolliset sairauskertomustiedot. Samanaikaisia muita psykiatrisia häiriöitä selvitettiin puolistrukturoiduilla diagnostisilla haastattelumenetelmillä (DSM-Axis I Disorders, SCID-I/P; DSM-IV Axis II Disorders, SCID-II). Itsetuhokäyttäytymistä selvitettiin sairauskertomustiedoista, haastattelemalla ja Scale for Suicidal Ideation – kysely-lomakkeella.

Koska PCV-DS:n tutkimusmenetelmät olivat vertailukelpoisia Vantaan depressiotutkimuksen (VDS) kanssa, PC-VDS:n vakavasta masennustilasta (MDD) kärsivien, 20-59-vuotiaiden potilaiden (N=79) kliinisiä ominaisuuksia voitiin verrata VDS:n psykiatristen avohoitopotilaiden (N=223) ja sairaalapotilaiden (N=46) ominaisuuksiin.

Seurannassa PC-VDS:n potilaita tutkittiin 3, 6 ja 18 kuukauden kuluttua. Koko seurantaan osallistui 123 potilasta (90%). Indeksimasennusjakson kestoa ja masennustilan uusiutumisten tai uudelleenpuhkeamisten ajoittumista tutkittiin yksityiskohtaisen graafisen elämänkaarikäyrän (life-chart) avulla.

Alkututkimuksessa osoittautui, että useimmilla potilailla (66%) oli ajankohtainen MDD ja lähes kaikilla (90%) oli ollut MDD jossain elämänsä vaiheessa. Alkututkimuksessa 34% potilaista poti "lieviä masennusoireita", jotka eivät täyttäneet ajankohtaisen MDD:n kriteereitä. Heistä kahdella kolmasosalla oli ollut vakava masennusjakso, mutta tutkimushetkellä he olivat joko jo osittain toipuneet siitä tai mahdollisesti heille oli puhkeamassa uusi MDD:n jakso. Tutkimuksessa MDD:t olivat yleensä toistuvia ja kroonisuus oli tavallista. Depressioon liittyi oheissairautena psykiatrinen akseli I:n häiriö 59 % potilaista, 52 % oli persoonallisuushäiriö ja 47 % krooninen fyysinen sairaus; vain 12 % ei ollut mitään oheissairauksia.

Tutkimuspotilaista kuudesosa (17%) oli yrittänyt itsemurhaa, lisäksi kolmannes (37 %) oli vakavasti harkinnut sitä. Itsetuhoista käyttäytymistä ilmeni lähinnä niillä, joilla oli keskivaikea tai vaikea MDD, persoonallisuushäiriö sekä aiempi erikoissairaanhoitotasoinen psykiatrinen hoito. Suurin osa oli saanut nykyiseenkin masennusjaksoon terveyskeskuksessa hoitoa, mutta itsemurha-ajatukset olivat jääneet pääosin tunnistamatta siellä.

PTH:n potilaiden ja psykiatrisen erikoissairaanhoitoon otettujen potilaiden vertailu paljasti, että suurin osa itsetuhoisista tai psykoottisista MDD-potilaista oli erikoissairaanhoidon piirissä ja että kaikkein vakavimmin oireilevat ja toimintakykynsä menettäneet potilaat olivat sairaalahoidossa.

Muiden kliinisten ominaisuuksien suhteen PTH:n ja psykiatrisen avohoidon MDD-potilaat olivat yllättävän samankaltaisia. Monella nyt PTH:n hoidossa olevalla MDD-potilaalla osoittautui olleen nykyisen masennustilajakson aikana erikoissairaanhoitotason psykiatrinen hoitokontakti.

Seurantatutkimuksessa korostui PTH:n depression kroonisuus ja toistuvuus. Puolentoista vuoden aikana vain neljännes MDD-potilaista pysyi toipumisen jälkeen oireettomana, kun taas toisella neljänneksellä toipuminen ei käynnistynyt lainkaan. Muut potilaat joko kärsivät depression jäännösoireista tai he sairastuivat uudestaan. Alkututkimuksessa kartoitetuista ilmiöistä parhaiten toipumista ennusti masennusoireiden vaikeusaste; myös päihdeongelmat, krooniset fyysiset sairaudet ja C-ryhmän persoonallisuushäiriöt ennustivat huonoa toipumista.

Tämän tutkimuksen perusteella PTH:n potilaiden lievätkin masennusoireet saattavat usein ilmentää sairastetun MDD:n jäännösoireita ja edellyttää hoidon arviointia. Itsemurhien ehkäisyn kannalta korkean riskin potilaiden itsetuhoiset ajatukset pitäisi depression hoidon yhteydessä tunnistaa paremmin. Depression hoitomalleja suunniteltaessa tulee huomioida PTH:n depression runsas toistuvuus ja kroonistuminen, jolloin kirjallisuuden mukaan tarvitaan mm. hoidon seurantaan erikoistunutta henkilökuntaa ja PTH:n ja erikoissairaanhoidon saumatonta yhteistyötä. Sen lisäksi myös mielekkääseen työnjakoon tulee panostaa, jotta depressiopotilaat saavat mahdollisimman tehokasta apua.

Avansanat: depressio, masennusoireet, perusterveydenhuolto, terveyskeskus

ABBREVIATIONS

AHCPR	Agency for Health Care Policy and Research
APA	American Psychiatric Association
AUDASIS-IV	Alcohol Use Disorder and Associated Disabilities Interview Schedule – DSM-IV Version
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
CDS	Collaborative Depression Study
CES-D	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CIDI-PHC	Composite International Diagnostic Interview-Primary Health Care Version
CRF	Corticotrophin Releasing Factor
DEPS	Depression Scale
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECA	Epidemiological Catchment Area Study
EU	European Union
ESEMeD	European Study of the Epidemiology of Mental Disorders
GAD	Generalized Anxiety Disorder
GHQ	General Health Questionnaire
GHQ-12	General Health Questionnaire with 12 items
30-GHQ	General Health Questionnaire with 30 items
GHS-MHS	German National Health Interview and Examination Survey
HAMD	Hamilton Rating Scale for Depression
HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratio
HS	Beck Hopelessness Scale
HSCL	Hopkins Symptom Checklist
5-HT	5-hydroxytryptamine (Serotonin)
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases, 10th Edition
IDS	Inventory of Depressive Symptoms
IMPACT	Improving Mood-Promoting Access to Collaborative Treatment
LIFE	Longitudinal Interval Follow-up Evaluation
M-CIDI	Michigan Revision of the Composite International Diagnostic Interview

MDD	Major Depressive Disorder
MDE	Major Depressive Episode
MinD	Minor Depression
MOS	Medical Outcome Study
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey Replication
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NICE	National Institute for Clinical Excellence
NIMH	National Institute of Mental Health
NIMH-CDS	National Institute of Mental Health Collaborative Depression Study
NNT	Number Needed to Treat
NPHS	Canadian National Population Survey
NSMHWB	National Survey of Mental Health and Well-Being
OR	Odds Ratio
PC-VDS	Vantaa Primary Care Depression Study
PMCD	Peijas Medical Care District
PPGHC	Psychological Problems in General Health Care
PROSPECT	Prevention of Suicide in Primary Care Elderly: Collaborative Trial
PRIME-MD	Primary Care Evaluation of Mental Disorders
PSE	Present State Examination
PSSS-R	Perceived Social Support Scale – Revised
RBD	Recurrent Brief Depressive Disorder
SCAN	Schedules for Clinical Assessment of Neuropsychiatry
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SCID-I/P	Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition
SCID-II	Structured Clinical Interview for DSM-IV AXIS II Disorders
SCL	Symptom Checklist
SD	Standard Deviation
SOFAS	Social and Occupational Functioning Assessment Scale for DSM-IV
SPSS	Statistical Package for the Social Sciences for Windows
SSI	Scale for Suicidal Ideation
SSRI	Serotonin-Selective Reuptake Inhibitor
subMDD	Subsyndromal Depression
STAR*D	Sequenced Treatment Alternatives to Relieve Depression Study
TADEP	Tampere Depression Study
U.K.	United Kingdom
UM-CIDI	The University of Michigan Revision of the Composite International Diagnostic Interview
U.S.	United States of America
USPSTF	U.S. Preventive Services Task Force
VDS	Vantaa Depression Study
WHO	World Health Organization
WMH-CIDI	World Mental Health version of Composite International Diagnostic Interview

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1 ABSTRACT

The Vantaa Primary Care Depression Study (PC-VDS) is a naturalistic and prospective cohort study concerning primary care patients with depressive disorders. It forms a collaborative depression research project between the Department of Mental Health and Alcohol Research of the National Public Health Institute, and the Primary Health Care Organization of the City of Vantaa. The aim is to obtain a comprehensive view on clinically significant depression in primary care, and to compare depressive patients in primary care and in secondary level psychiatric care in terms of clinical characteristics relating to treatment needs.

Consecutive patients (N=1111) in three primary care health centres were screened for depression with the PRIME-MD, and positive cases interviewed by telephone. Cases with current depressive symptoms were diagnosed face-to-face with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P). A cohort of 137 patients with unipolar depressive disorders, comprising all patients with at least two depressive symptoms and clinically significant distress or disability, was recruited. The Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), medical records, rating scales, interview and a retrospective life-chart were used to obtain comprehensive cross-sectional and retrospective longitudinal information. For investigation of suicidal behaviour the Scale for Suicidal Ideation (SSI), patient records and the interview were used.

The methodology was designed to be comparable to The Vantaa Depression Study (VDS) conducted in secondary level psychiatric care. Comparison of major depressive disorder (MDD) patients aged 20-59 from primary care in PC-VDS (N=79) was conducted with new psychiatric outpatients (N=223) and inpatients (N=46) in VDS.

The PC-VDS cohort was prospectively followed up at 3, 6 and 18 months. Altogether 123 patients (90%) completed the follow-up, including 79 with baseline MDD and 44 with baseline subsyndromal disorders. Duration of the index episode and the timing of relapses or recurrences were examined using a life-chart.

The retrospective investigation revealed current MDD in most (66%), and lifetime MDD in nearly all (90%) cases of clinically significant depressive syndromes. Two thirds of the "subsyndromal" cases had a history of major depressive episode (MDE), although they were

currently either in partial remission or a potential prodromal phase. Recurrences and chronicity were common. The picture of depression was complicated by Axis I co-morbidity in 59%, Axis II in 52% and chronic Axis III disorders in 47%; only 12% had no co-morbidity.

Within their lifetimes, one third (37%) had seriously considered suicide, and one sixth (17%) had attempted it. Suicidal behaviour clustered almost exclusively in patients with moderate to severe MDD, co-morbidity with personality disorders, and a history of treatment in psychiatric care. The majority had received treatment for depression, but suicidal ideation had mostly remained unrecognised.

The comparison of patients with MDD in primary care to those in psychiatric care revealed that the majority of suicidal or psychotic patients were receiving psychiatric treatment, and the patients with the most severe symptoms and functional limitations were hospitalized. In other clinical aspects, patients with MDD in primary care were surprisingly similar to psychiatric outpatients. Mental health contacts earlier in the current MDE were common among primary care patients.

The 18-month prospective investigation with a life-chart methodology verified the chronic and recurrent nature of depression in primary care. Only one-quarter of patients with MDD achieved and maintained full remission during the follow-up period, while another quarter failed to remit at all. The remaining patients suffered either from residual symptoms or recurrences. While severity of depression was the strongest predictor of recovery, presence of co-morbid substance use disorders, chronic medical illness and cluster C personality disorders all contributed to an adverse outcome.

In clinical decision making, beside severity of depression and co-morbidity, history of previous MDD should not be ignored by primary care doctors while depression there is usually severe enough to indicate at least follow-up, and concerning those with residual symptoms, evaluation of their current treatment. Moreover, recognition of suicidal behaviour among depressed patients should also be improved. In order to improve outcome of depression in primary care, the often chronic and recurrent nature of depression should be taken into account in organizing the care. According to literature management programs of a chronic disease, with enhancement of the role of case managers and greater integration of primary and specialist care, have been successful. Optimum ways of allocating resources between treatment providers as well as within health centres should be found.

Keywords: depression, primary care, subsyndromal depression

2 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I Vuorilehto MS, Melartin TK, Isometsä ET:
Depressive disorders in primary care: recurrent, chronic, and co-morbid.
Psychol Med. 2005 May;35(5):673-82.

II Vuorilehto MS, Melartin TK, Isometsä ET:
Suicidal behaviour among primary-care patients with depressive disorders.
Psychol Med. 2006 Feb;36(2):203-10.

III Vuorilehto MS, Melartin TK, Rytsälä HJ, Isometsä ET:
Do characteristics of patients with major depressive disorder differ between primary and psychiatric care?
Psychol Med. 2007 Jun;37(6):893-904.

IV Vuorilehto MS, Melartin TK, Isometsä ET:
Course and Outcome of Depressive Disorders in Primary Care:
A Prospective 18-month Study
(submitted in Psychol Med.)

3 INTRODUCTION

The word depression refers to a sense of lowering, the feeling of being pressed down, and the experience of loss (the de-prefix implying deletion of something – of interest, of hope, of energy) (Oxford English Dictionary). These meanings suggest a lack of interest in habitual activities, an inability to experience pleasure and feeling of personal worthlessness. Disappointment, loss or other painful events in life commonly cause self-limited depressive affects or feelings which mostly do not interfere with a person's functional capacity, unless becoming longer lasting.

The concept of depression as a medical condition appeared in medical literature in Robert Burton's Anatomy of Melancholy in 1621. He described in detail the psychological and social causes, such as poverty, fear and solitude, that were associated with melancholia. Now for a few decades, especially within those branches of medicine connected with mental health – mainly psychiatry and general practice – depression as a medical condition has been in the focus in the development of practice guidelines and treatment programs. This has been promoted by governments in public campaigns such as The Ostrobothnia Project in Finland and the European Alliance against Depression.

Compared with other medical diagnoses, depressive disorders are common; every sixth person will suffer from major depressive disorder during their lifetime, women twice as often as men. It is especially common in many non-psychiatric medical settings, such as inpatients wards and in chronically ill patients. Although depressive symptoms in many people recover rapidly, the likelihood of a new episode of depression is high and increases after every new episode. A significant minority of patients will suffer from persistent depression. Considering this, managing depression as a chronic disease should be considered an option in health care systems.

Depression has a considerable impact on the lives of those who experience it and their families, and also has a substantial economic effect on society. Even milder depressive disorders impair the functional capacity, leading to difficulties in social and marital relations, or in work. Another crucial aspect is the increased mortality associated with depression. This is usually a result of suicide, though the risk of premature death in cardiovascular diseases is also elevated. The total number of suicides in many countries exceeds the traffic mortality and amounts to near one million every year in the world. By the year 2020, depression is assumed to have an effect on disability and mortality second only to cardiovascular disease.

Treating depression effectively is therefore essential. Even in Europe, however, only a minority of those with major depression seeks or receives treatment. Although the severity of depression correlates with the probability of treatment, only about half of persons

with serious depression in developed countries and a quarter in less-developed countries receive treatment. Furthermore, the quality of offered treatment is suboptimal especially in primary care. Any discussion of the epidemic rise in prescriptions of antidepressants together with popular scepticism towards antidepressant treatments has to be considered against this background.

In the aspect of public health, primary health care clearly acts as the basis for the care of depression. Primary health care provides keys for promoting health and preventing disease among regularly seen patients and serves as the basis for early detection, intervention and long-term disease management. Most national suicide prevention strategies challenge primary care to improve detection and management of depression. Referral to psychiatric care is commonly recommended only for a minority of patient groups in need of ambulatory services or with characteristics related to poor prognosis. Therefore, depression in primary health care should form a priority area of depression research.

The Vantaa Primary Care Depression Study (PC-VDS) is a prospective, naturalistic cohort study of 137 primary care patients with depressive disorder. In the PC-VDS the clinical characteristics of patients with depression are investigated and predictors of chronicity, recurrences and suicidal behaviour are assessed. The present thesis focuses on current co-morbidity and suicidal behaviour in depressive primary care patients and compares them with secondary care psychiatric patients. It also investigates the outcome among depressive patients followed up for 18 months.

4 REVIEW OF THE LITERATURE

4.1 Depression as an affect

The term depression in everyday language covers a wide range of meanings from the temporary decrease of mood to deeply impaired, even life-threatening disorders. Disappointment, loss or other painful events in life may all serve as trigger for depressive affects or feelings which are self-limited and do not usually significantly interfere with a person's functional capacity, unless becoming longer lasting. It has been postulated that in some situations depressive affect might even be an evolutionary useful reaction in redefinition of goals and reallocation of efforts (Nesse et al., 2006). As used in this thesis, depression refers to a constellation including not only mood, but also physical, mental and behavioural experiences that define more prolonged, impairing and severe conditions that may be clinically diagnosable as a syndrome of depression. Depressed people may differ from one another by the number, unique patterns and severity of symptoms, but in all depressive disorders some features are present from the domains of affect, cognition, behaviour and physical functioning.

4.2 Psychiatric diagnoses and their validity

Classification and subtyping of diseases, that is, diagnoses, serve the purposes of etiologic research, prognosis and prediction of treatment response. Explicit psychiatric diagnostic criteria, since the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III) (APA, 1980) became a norm in research, provided a universal language in teaching, and improved communication between the users of psychiatric services, caregivers and society at large. The reliability of diagnoses in clinical practice improved hugely with the introduction of explicit definitions (Kendell et al., 2003).

Although reliability is a necessity, it is not a sufficient precondition to validity (Kendell et al., 2003). While it may be appropriate to base epidemiological research and treatment trials on syndromes in clinical use with no proofs of validity, etiologic research needs valid criteria (Kendell et al., 2003). In psychiatry, criteria of validity of a diagnosis can be described as follows: 1) *antecedent validators* (familiar aggregation, premorbid personality, demographic factors, precipitating factors), 2) *concurrent validators* (symptom profiles, psychological tests, biological markers), 3) *predictive validators* (diagnostic stability over time, outcome, response to treatment) and 4) *delimitation* from other disorders (Kendell et al., 2003).

Most of the specifically delineated disorders captured in current diagnostic classifications, however, are not completely discrete entities with absolute boundaries that separate them from other disorders (Kendell et al., 2003). The categorical diagnoses are likely to represent a heterogeneous set of disorders that are derived from a wide range of etiological and genetic factors (Charney et al., 2004). In attempting to solve this problem, some researchers suggest new, narrower or broader borders for mood disorders. Others suggest dimensional measuring of narrow symptoms instead of syndromes (Angst et al., 1997).

4.3 Diagnosis of depressive disorders

Research programmes, such as this thesis, usually apply the DSM classification rather than the International Classificaton of Disease (ICD) (WHO) as it provides more detailed guidelines for case definition. According to DSM-IV (APA, 1994) depressive disorders take one of three forms: major depressive episode (MDE), dysthymic disorder or "depression not otherwise specified", which includes several forms of briefer or milder periods of depression. Major depressive disorder (MDD) consists of one or more MDE (Figure 1.).

MDE may be classified as mild, moderate or severe (with or without psychotic features), based on the number and severity of symptoms, and the degree of functional disability and distress (APA, 1994, 2000). DSM-IV and ICD-10 diagnoses of MDD differ slightly: in ICD-10 the core symptoms are added with loss of energy and two of the three core symptoms have to be present. Also worthlessness and inappropriate guilt are defined as separate symptoms.

Dysthymic disorder in DSM-IV consists of chronic but milder symptoms than MDE (Figure 2.).

Figure 1. The diagnostic criteria for Major Depressive Episode in DSM-IV (APA, 1994).

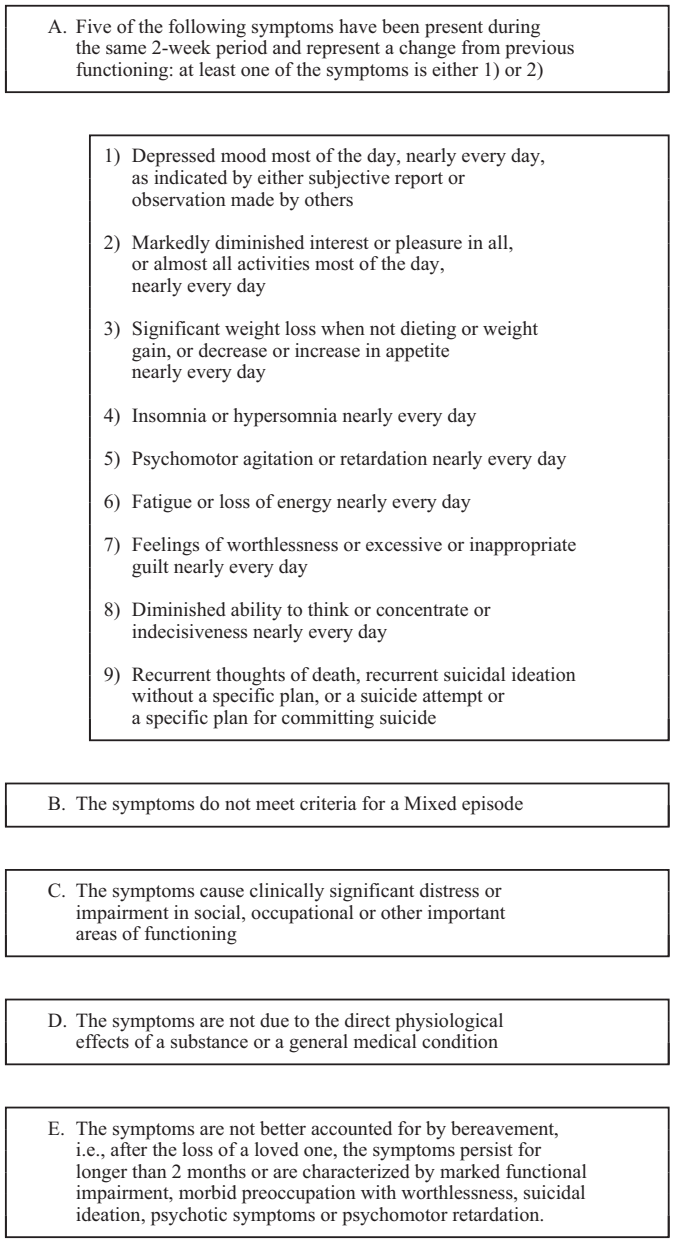
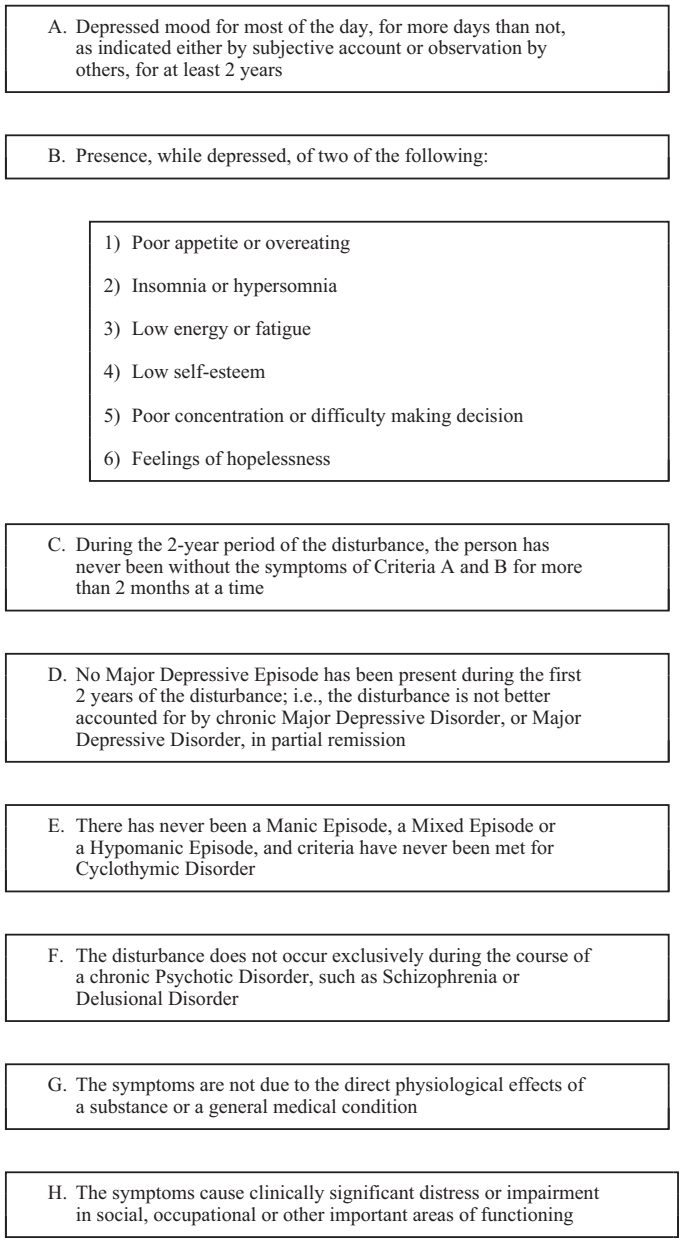


Figure 2. The diagnostic criteria for Dysthymic Disorder in DSM-IV (APA, 1994).



Moreover, a substantial proportion of subjects with disabling depressive symptoms fail to meet the diagnostic criteria for MDD or dysthymia, as demonstrated in many studies on primary care patients, such as the World Health Organization (WHO) study on Psychological Problems in General Health Care (PPGHC) (Sartorius et al., 1996). Some of these subsyndromal conditions are included in the category Depressive disorder not otherwise specified (APA, 1994). In literature the use of the terms describing subsyndromal depressions is unfortunately diverse, including syndromes with varying numbers of symptoms, with varying duration and causing varying degrees of impairment (Pincus et al., 1999).

Subsyndromal depressive symptoms, although not a diagnostic entity, is a clinical condition proposed by Judd in order to further analyse the pleomorphism of the depressive spectrum in the National Institute of Mental Health (NIMH) Epidemiological Catchment Area (ECA) Program (Judd et al., 1997). It was there defined as "at least two current depressive symptoms, present every day for most of the time, at least two weeks, in persons not meeting criteria for MDD, minor depression or dysthymic disorder". Thus it could refer to residual symptoms of a past MDE or a prodromal of a future MDE (Judd et al., 1997). In this thesis the definition suggested by Judd (1997) is used for subsyndromal depressive disorder with one exception of demanding one of the current symptoms to be a core symptom of MDE.

For *minor depression* (MinD), although not considered an official clinical diagnosis, the American Psychiatric Association defined research diagnostic criteria in Appendix B of the DSM-IV (APA, 1994). The essential features are identical to MDE in duration, but involve fewer symptoms and less impairment. An episode involves either sad or depressed mood or loss of interest or pleasure in nearly all activities. In total, at least two but less than five additional symptoms must be present.

The Appendix B in DSM-IV (APA, 1994) also defines diagnostic criteria for *recurrent brief depressive disorder*, where the episodes are identical to MDE in the number and severity of symptoms but do not meet the 2-week duration requirement. The episodes last at least 2 days but less than two weeks. Episodes must recur minimum once a month for a period of 12 consecutive months (APA, 1994).

4.3.1 Subgroups of depressive disorders

Diagnostic specifiers in DSM-IV define descriptively important distinctive features of depressive episode for the purposes of research or treatment choice (APA, 1994). *Psychotic features* may be present in a severe MDE, and includes presence of either hallucinations or delusions. Psychotic depression, even more than melancholic depression, appears to be relatively stable over repeated episodes (Coryell et al., 1994). *Melancholic features* of DSM-IV MDE include lack of reactivity to pleasurable stimuli, diurnal variation of symptoms, inappropriate guilt, early morning awakening, marked psychomotor change, either retardation or agitation, and significant loss of appetite or weight loss. According to Parker (Parker et al., 2005) melancholic features and psychotic features may represent a distinctive form of severe depression arising from different pathophysiology than other forms of depression. Depression with *atypical features* was first recognized in a subset of patients with depression who preferentially responded to the monoamine oxidase inhibitors in contrast to patients with melancholic depression (Stewart et al., 2007). Atypical features include mood reactivity and two or more of the following: increased appetite or weight gain, hypersomnia, leaden paralysis and long-standing interpersonal rejection sensitivity in non-psychotic, non-melancholic MDE or dysthymic disorder (APA, 1994). The current definition of atypical features appears problematic as interpersonal rejection sensitivity and leaden paralysis may have their phenomenological base in anxiety rather than depression (Parker et al., 2002). *Seasonal pattern* depressions have an apparent regular onset and disappearance during certain times of the year. In the Northern hemisphere the most common pattern is autumn or winter depressions (APA, 1994). *Postpartum onset* specifier can be applied to a MDE if the onset is within 4 weeks after the delivery of a child (APA, 1994).

4.3.2 Multiaxial assessment

Multiaxial system of DSM-IV (APA, 1994) involves an assessment on several axes, each of which refers to a different domain of information that may help the clinician plan treatment and predict outcome. In this thesis Axis I (clinical disorder), Axis II (personality disorder) and Axis III (general medical condition) are used.

4.4 Epidemiology of depressive disorders

4.4.1 Prevalence of depressive disorders in population samples

4.4.1.1 Prevalence of MDD and dysthymia

Depressive disorders are common and distributed widely around the world (Ayuso-Mateos et al., 2001, Alonso et al., 2004a, Demyttenaere et al., 2004). International prevalence comparisons should, however, be made with caution, as methodological differences, among others, render incompatibilities across available epidemiological studies (Patten, 2003). Even the portability of MDD diagnostic criteria across countries has been questioned (Patten, 2003).

The lifetime risk for MDD appears to be about 15% in the majority of large population surveys such as The National Comorbidity Survey (NCS) (Kessler, 1994), the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Bijl et al., 1998), the National Comorbidity Survey Replication (NCS-R) (Kessler et al., 2003), the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Hasin et al., 2005) and the European Study of the Epidemiology of Mental Disorders (ESEMeD) (Alonso et al., 2004a). Exceptionally low prevalence of MDD has been reported from Taiwan (1.5%) due at least partly to stigma and high prevalence in Lebanon (19%) during war (Weissman et al., 1996). The prevalence for females is about twice as high as for males (Paykel et al., 2005); it is fairly low until early teens, when it begins to rise in roughly linear fashion (Kessler, 1994), the median age of onset being around 30 years (Kessler et al., 2003).

Table 1. Demonstrates the large variation of one-year prevalence of MDD across studies and sites. In 27 European studies Wittchen (2005) found variation from 3.1% to 10.1% (median 6.9%) (Wittchen et al., 2005). Even minor modifications in the diagnostic procedure, such as CIDI vs. UM-CIDI, can lead to large changes in the results (Patten, 2003) as seen when comparing the Ontario Health Survey in Canada (Parikh et al., 1999) and the NCS in U.S. (Kessler, 1994) (Table 1.).

Table 1. One year prevalences of Major Depressive Disorder in representative national or multinational population surveys.

Study (source)	Country year	Sample size	Diagnostic instrument	Taxonomy	Age group	Prevalence %
ECA (Eaton et al., 2007)	U.S. 1981	175 211	DIS	DSM-III	18+	2.8
NCS (Kessler et al., 1994)	U.S. 1990-1992	9 282	CIDI	DSM-IIIR	15-54	8.6
Ontario Health Survey (Parikh et al., 1999)	Canada 1991	13 002	UM-CIDI	DSM-IIIR	15-64	4.1
NEMESIS (Bijl et al., 1998)	Netherlands 1996	7 076	CIDI	DSM-IIIR	18-64	5.8
NSMHWB (Andrews et al., 2001)	Australia 1997	1 061	CIDI	DSM-IV	18+	6.3
GHS-MHS (Jacobi et al., 2004)	Germany 1999	4 181	M-CIDI	DSM-IV	18-65	8.3
Health 2000 (Pirkola et al., 2005)	Finland 2000	6 005	M-CIDI	DSM-IV	30+	3.4
ESEMeD (Alonso et al., 2004)	6 European countries 2000-2002	21 425	WMH-CIDI	DSM-IV	18+	3.9
NESARC (Hasin et al., 2005)	U.S. 2001-2002	43 000	AUDASIS-IV	DSM-IV	18+	5.3
NCS-R (Kessler et al., 2003)	U.S. 2001-2003	9 090	CIDI	DSM-IV	18+	6.6

In Finland, the Finnish Health Care Survey in 1996 reported a higher one-year prevalence of MDE (9.3%) (Lindeman et al., 2000) than the Health 2000 project four years later (Pirkola et al., 2005c). The differences may be explained by methodological factors including differences in diagnostic interview and age frames (Pirkola et al., 2005c) (Table 1.). Older age, marriage and employment predicted in Finland lower prevalence (Pirkola et al., 2005c).

Dysthymic disorder has been scarcely studied in large surveys: one-year prevalence was 1.1% in the Australian National Survey of Mental Health and Well-Being (NSMHWB) (Andrews et al., 2001) and current dysthymia was found in 1.5% of the U.S. general population in ECA (Judd et al., 1997). In a Finnish computer-assisted telephone interview a 6-month prevalence of dysthymia was about 2% (Isometsä et al., 1997).

4.4.1.2 Prevalence of subsyndromal depressive disorders

The amount of depressive symptoms in the general population appears high (Cuijpers et al., 2004). Reporting compatible prevalence rates, however, is difficult because of the high variation in the criteria used for subsyndromal depressions or amount of minimum symptoms required for inclusion in the available studies (Pincus et al., 1999). With use of the definition in ECA, "two or more symptoms of depression and does not meet criteria of MDD, dysthymia or MinD", 12-month prevalence of 8.4% and current prevalence of 3.9% were obtained for subsyndromal depressive disorders in ECA (Judd et al., 1997). Judd has suggested that two classes of subsyndromal depressive disorders exist in community: one, which occurs as a component of the course of MDD; and another occurring spontaneously in non-MDD subjects (Judd et al., 1994). In the first instance subsyndromal depression may be prodromal to episodes of MinD or MDD or residual to resolving episodes (Judd et al., 1994, Judd et al., 1997)

Lifetime MinD (2 to 4 symptoms of MDD without a lifetime history of either MDD or dysthymia) was found in 10% of the respondents in the NCS (Kessler et al., 1997), one-year MinD in 7.5% in the NEMESIS and current MinD in 1.5% in ECA (Judd et al., 1997).

4.4.2 Use of services for depression in population samples

Information about health service-use offered by epidemiological studies may increase our capacity to assess how well recourses are allocated to meet treatment needs (Demyttenaere et al., 2004). Evidence suggests that the majority of individuals with MDD receive no treatment either in Finland or elsewhere (Demyttenaere et al., 2004, Hämäläinen et al., 2004). The reasons for this are not well known. For exact analyses on help seeking behaviour and on the factors relating to service-use, even large epidemiological surveys often lack statistical power to disentangle differences in subgroups (Hämäläinen et al., 2004).

Although the majority of individuals with MDD consult their primary care doctors for general health problems (Parikh et al., 1997), only about a third of them communicate their depression to a health care professional (Parikh et al., 1997, Galbaud du Fort et al., 1999, Hämäläinen et al., 2004, Wittchen et al., 2005).

The decision of seeking help seems to associate with higher disability and long-lasting, severe symptomatology (Fortney et al., 1998, Hämäläinen et al., 2004, Hämäläinen et al., 2008) such as suicidal thoughts (Galbaud du Fort et al., 1999) and co-morbid other psychiatric disorders (Fortney et al., 1998, Galbaud du Fort et al., 1999), (Hämäläinen et al., 2008) or co-morbid medical illnesses (Lin et al., 1998). Furthermore, attributing the perceived distress to a mental health problem (Lin et al., 1998, Hämäläinen et al., 2004), as well as personal attitudes such as feeling comfortable consulting a mental health professional (Lin et al., 1998) may influence on help-seeking decision.

Even of those whose presenting complaint is depression, less than a half receive treatment for it (Bebbington et al., 2000), and especially in primary care, the treatment is seldom optimal (Bebbington et al., 1997). Although severity of depression correlates with probability of treatment, from a third to two thirds of persons with serious depression in developed countries, and more than three quarters in underdeveloped countries, receive no treatment (Demyttenaere et al., 2004).

The majority of service-use is distributed among primary care services and specialist services; of them primary care represents the basic level of health care system where consumers may bring any heath problems - physical, mental, emotional or social at visits to a general practitioner, family physician or company doctor. Specialty care in surveys is usually defined as comprising the visits to a psychiatrist, psychologist, hospital psychiatric emergency room, psychiatric outpatient clinic, mental health centre, drug or alcohol outpatient clinic or inpatient drug clinic.

In epidemiological surveys individuals with MDD usually report having received treatment twice as often in specialist care as in primary care (Alonso et al., 2004b, ten Have et al., 2004, Hämäläinen et al., 2008), (Parikh et al., 1997). The choice of service provider may be influenced by sociodemographic factors, such as age and educational background (Parikh et al., 1997, ten Have et al., 2004, Hämäläinen et al., 2008), by the co-morbidity and severity of depression and suicidal behaviour (ten Have et al., 2004), (Hämäläinen et al., 2008) and also by the availability of services (Fortney et al., 1998).

4.4.3 Public health impact of depressive disorders

Besides being a cause of human suffering, MDD is an important global public health issue; depression was rated as the fourth leading cause of disease burden worldwide in 1990 (Murray et al., 1997b).

Depression has the tendency to assume a recurrent or chronic course, and over time to be associated with increasing disability (Solomon et al., 2000, Andrews, 2001). Today in Finland, depression is a major cause of permanent disability pension (Salminen et al., 1997). Moreover, studies on family relationships have indicated significant impairment of parental role in persons with depression (Goodman, 2007); children of depressed parents are at a high risk for developing depression or other disorders themselves (Lieb et al., 2002). Depression may even produce greater decrement in health compared with most chronic diseases, such as coronary heart disease, arthritis, asthma, or diabetes (Hays et al., 1995).

Death by suicide is the most important complication of depression. In Finland suicide is the leading cause of death among those under the age of 35 years (Tilastokeskus, 2008). Suicide also means a major loss of expected active life years and a huge stress and long-term burden to the families of the victims of suicide. Moreover, attempted suicides are one of the main causes for costly visits into emergency rooms of general hospitals (Yeo, 1993).

The co-morbidity of depression with chronic physical diseases such as coronary heart disease and diabetes is well recognized (Benton et al., 2007). The co-morbid state of depression incrementally worsens health compared with depression alone, with any of the chronic diseases alone and with any combination of chronic diseases without depression (Benton et al., 2007). With a growing elderly population, and the associated increase in prevalence of chronic medical conditions, a concomitant rise in the prevalence of depression is to be expected. In fact, projections indicate that after heart disease, depression is expected to become the second leading cause of disease burden by the year 2020 (Murray et al., 1997a).

These results indicate the urgency of addressing depression as a public health priority to reduce disease burden and disability, and to improve the overall health of populations (Moussavi et al., 2007).

4.4.4 Prevalence of depressive disorders in clinical patient samples

4.4.4.1 Prevalence of depressive disorders in primary care and psychiatric care

The widest epidemiological clinical study so far on depressive disorders in primary care has been the WHO PPGHC study in the mid-nineties (Sartorius et al., 1993), comprising 14 countries and 26 000 primary care patients around the world. In the prevalence of current depressive disorders it found a 15-fold variation across countries (Simon et al., 2002) (Table 2.). Whether the variation represents true differences in prevalences, it could perhaps be caused by ethnic differences in vulnerability to depression and community-level differences in exposure to stressors or traumatic events (Simon et al., 2002). The variation may, however, represent problems with definition and measurement: the depressive disorders defined in U.S. and Western Europe may exist in different forms in other cultures, and identical diagnostic methods may identify different levels of severity of depression due to linguistic or cultural differences in the tendency to report distress (Mezzich et al., 1999).

In the WHO PPGHC an average of 10% of patients in primary care appeared to suffer from current MDE and 2% from dysthymia based on ICD-10 taxonomy (Sartorius et al., 1996). Comparable prevalences have been found in smaller studies (Olfson et al., 1996). In Finland, the Tampere Depression (TADEP) Study found clinical depression in a tenth of primary care patients; it also found clinical depression in one-half of patients in community mental heath centres (Salokangas et al., 1996).

Patients seen in primary care often represent the less severe end of the disease spectrum. They might be at the early stages of the illness, with less differentiated signs and symptoms (Alegria, 2000) and therefore their depressive symptoms may fail to achieve the diagnostic threshold for MDE or dysthymia. The prevalence of subsyndromal depressive symptoms in a review of 36 primary care studies varied from 5% to 16% depending on the definition of the condition (Pincus et al., 1999). The WHO PPGHC reported subsyndromal symptoms (four symptoms of ICD-10 MDD criteria, one of which a core criteria) in 7% of primary care patients (Sartorius et al., 1996); in a subsample, brief recurrent depression lasting 3-4 days was found in 10% (Weiller et al., 1994). In a study comprising one thousand primary care patients in U.S., 9% of individuals suffered from depressed mood or anhedonia lasting at least two weeks (Olfson et al., 1996). In the Finnish TADEP study, beside clinical depression, little less than 10% had some depressive symptoms (Salokangas et al., 1996).

Table 2. Prevalences of ICD-10 Major Depressive Disorders in the study centres of the WHO Psychological Problems in General Health Care study (Simon et al., 2002).

City	Interviewed N	Weighted prevalence %	Confidence interval 95%
Nagasaki	336	1.6	0.7-2.5
Shanghai	576	2.5	1.6-3.4
Ibadan	269	4.0	2.6-5.5
Verona	250	4.6	2.9-6.3
Berlin	400	5.3	3.9-6.7
Seattle	373	6.4	4.6-8.2
Athens	196	7.3	4.6-9.9
Bangalore	398	8.6	6.1-11.1
Mainz	400	9.9	6.6-13.1
Ankara	400	10.7	7.7-13.7
Paris	405	13.5	0.9-16.0
Groningen	340	14.4	11.3-17.6
Manchester	428	17.1	14.4-19.8
Rio de Janeiro	393	18.3	14.2-22.3
Santiago	274	26.3	16.9-35.8

4.4.4.2 Prevalence of depressive disorders in medically ill patients

Depression frequently occurs in the context of chronic medical illness (Stein et al., 2006), but only recent research in the community has attracted attention to the relationship between depression and chronic medical conditions. A doubled risk of MDD in medical conditions (e.g. migraine, sinusitis, back problems) was reported in medium term follow-up in the Canadian National Population Health Survey (NPHS) (Patten et al., 2005, Stein et al., 2006). Reports from general health care and specialist medical settings have also described a high amount of co-morbid depression although the information of the prevalences is inconsistent and suffers from selection bias (Alegria, 2000).

Of specific disease groups cardiovascular diseases have been an important focus of depression research: in acute coronary artery disease the prevalence of MDD appears to be from 15% to 23% (Glassman et al., 2002). Similar high prevalences of depression have been found among post stroke patients (Robinson, 2003). Furthermore, chronic pain seems to increase the risk of associating MDD the rate of which has been reported from 30% to 54% (Baune et al., 2008).

Several explanations for the association of MDD and chronic medical conditions have been proposed (Katon, 2003). Physical disease may cause depression either by biological or psychological mechanism. One possibility is that depression may decrease the ability of the individual to cope with limitations or symptoms (e.g. pain) imposed by the physical illness. It is also possible that the loss of function and independence associated with many chronic physical illnesses may cause depression.

4.5 Etiology and pathogenesis of depressive disorders

4.5.1 Multifactorial etiology

Depression is currently considered a complex, multifactorial disorder, where the risk factors from multiple domains are related and interacting with each other (Kendler et al., 2002, 2006). In the etiology of depression life stress appears an important component, but also requires other vulnerability factors to explain onset conditions (Monroe et al., 2001). A widely held view is that the combination of predisposing genetic factors, early life stress and ongoing stress may ultimately determine individuals' responsiveness to stress and the vulnerability to depression (Charney et al., 2004). For better understanding of the etiology and identifying the factors involved in the pathophysiology and treatment of depressive illness, more has to be known about the genetic vulnerability, neurochemistry, signal transduction mechanisms, neural circuits, psychosocial stressors and their complex interaction. Moreover it has to be remembered that while diagnosed on phenomenological basis, depression is likely to be an etiologically heterogeneous group of disorders (Hasler et al., 2004).

4.5.2 Heritability

Depressive disorders and symptoms run in families (Sullivan et al., 2000, Lewinsohn et al., 2003, Korszun et al., 2004). The heritability for depression is usually reported to be from 30% to 40%, but the more severely depressed clinical samples have been investigated the higher the heritability appears (McGuffin et al., 1996).

Slow progress in the genetic research on depression is anticipated while multiple genes are possibly involved and interacting with environmental factors (Caspi et al., 2003). Of special clinical interest are the candidate genes, which associate to the probability of patients to respond to particular treatments such as the 5-HT transporter gene and its allelic variation. An example of gene-by-environment interaction is Caspi's finding that a functional polymorphism in the promoter region of the 5-HT transporter gene moderates the influence of stressful life events on depression (Caspi et al., 2003).

4.5.3 Pathogenesis

The relationship between depression, modern antidepressant drugs and changes in levels of serotonin and noradrenaline in the brain is usually greatly oversimplified when presented to the public, at least partly due to the lack of specific scientific knowledge. Overall, in the etiology of mood disorders and action of antidepressants, a major role has been suggested for intracellular pathways regulating neuroplasticity and neurodegeneration (Popoli et al., 2002). These relate in a complex way to multiple hormonal changes including, among others, the disturbances in the regulation of corticotrophin releasing factor (CRF) and functional disturbances in hypothalamic-pituitary-adrenal (HPA)-axis as well as to brain-derived neurotrophic factor (BDNF) (Charney et al., 2004, Sapolsky, 2004, Castren, 2005).

While many brain regions have been implicated in regulating emotions we still have poor understanding of the neural circuitry underlying the normal mood or abnormalities of mood. It is likely that several brain areas, documented in brain imaging studies to show regional blood flow or metabolic changes, mediate diverse symptoms of depression (Nestler et al., 2002, Mayberg, 2003).

4.5.4 Environmental risk factors

Environmental risk factors for depression can be divided into distant and recent risk factors. The former include experiences from childhood and adolescence and the latter risk factors, such as stressful life events and poor social support, occurring in a defined period preceding the occurrence of MDE (Kendler et al., 2002, 2006).

4.5.4.1 Childhood experiences

The risk for adult MDD may be increased by a wide range of negative life events in childhood ranging from sexual abuse (Heim et al., 2000), to a disturbed family environment, such as poor parenting, parental loss or separation, and depression of parents (Tennant, 1988, Lieb et al., 2002, Veijola et al., 2004). Individuals may react to parenting and its shortcomings in different ways guided in part by genetically influenced characteristics e.g. temperament (Kendler et al., 2006).

Within the Health 2000 study in Finland, the impact of adverse environmental factors during childhood seemed to be composed of a wide range of factors from direct causal associations to complex interacting environmental effects (Pirkola et al., 2005a). In another Finnish study where depressiveness and childhood adversities alone and in combination with recent adverse events were studied, the consequences of an unfavourable childhood background seemed worse if combined with adult adverse life events (Korkeila et al., 2005).

4.5.4.2 Recent adverse life events and social support

Current stressful life events and difficulties form a major risk factor for MDD (Kendler et al., 2006). Different types of difficulties may lead to different depressive symptom profiles (Keller et al., 2007). Moreover, low social support appears to increase the risk of recurrent MDE (Kendler et al., 2006). A bidirectional model has been suggested, where partly genetically determined individual differences in personality appear to influence on the way in which individuals view the world around them and on the likeliness of experiencing stressful life events and on the quality of interpersonal relationships, which in turn "feed back" to them, influencing their risk for depression (Kendler et al., 2003). Of psychiatric patients often with complicated MDD, the majority attribute the onset of MDE to some adverse event, although no clustering of live events appeared to associate with the time of onset (Leskelä et al., 2004).

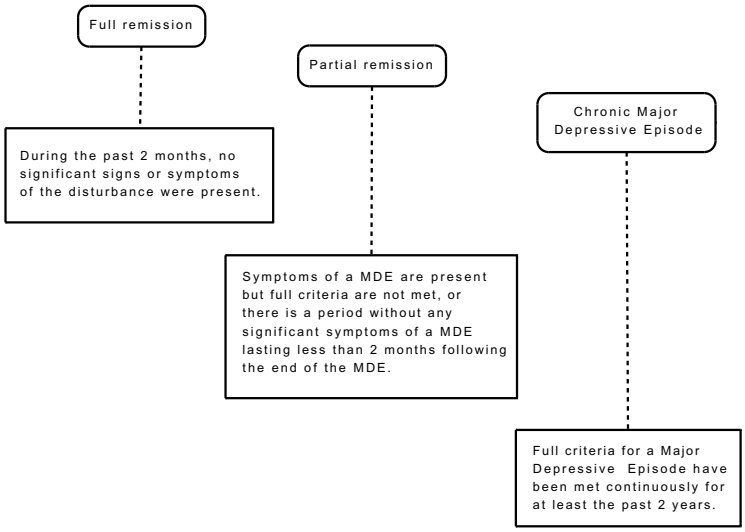
4.6 Course and outcome of depressive disorders

Research on the natural course of depressive disorders is essential for the understanding of the nature of depression. Epidemiological studies support the view that depression is dynamic in nature, evolving a continuum of depressive symptoms of varying severity and duration, and that individuals in this continuum move in and out of various diagnostic types of depression over time (Judd et al., 1997).

4.6.1 Methodological aspects in outcome studies

Interpreting reports on the course of depression and applying them to clinical practice suffer from inconsistently used descriptors for change points in the course of the illness (Frank et al., 1991, Keller, 2003). The terms in use across studies, such as relapse, recurrence and especially remission, refer to a varying number and duration of symptoms, despite the efforts taken to achieve a consensus on the terminology already in the early nineties (Frank et al., 1991). Remission as a result of treatment has been proposed to be defined as a completely asymptomatic state, with absence of all symptoms of depression and functional impairment (Keller, 2003) as any residual symptoms serve as a strong predictor of earlier relapse (Paykel et al., 1995, Judd et al., 1998) and impaired social functioning (Kennedy et al., 2004). In a substantial part of research, patients have been considered to be in remission despite exhibiting some minor symptoms (Keller, 1992). [In this thesis the criteria of DSM-IV are used: *relapse* refers to the return of symptoms fulfilling MDE criteria after a period of more than two weeks but less than two months with symptoms below the MDE threshold, *recurrence* refers to the return of MDE after at least two consecutive months of partial or full remission; the criteria for remission are shown in figure 3.]

Figure 3. DSM-IV criteria for Remission and Chronic Specifier for Major Depressive Episode (APA, 1994).



Moreover, primary care studies suffer from reporting only a cross-sectional outcome of depression i.e. reporting the status of the patient at the end of the follow-up period, thus ignoring relapses and recurrences during the follow-up. This limitation has been overcome in some studies on psychiatric patient populations, such as the NIMH-CDS (Keller et al., 1987) and VDS in Finland (Melartin et al., 2004) with use of life-chart methodology, based on multiple assessments during the longitudinal course of psychiatric disorders in sufficient detail to provide the basis for calculating length of episodes and time to remission (Keller et al., 1987).

4.6.2 Course and outcome of depressive disorders in population samples

In population surveys (ECA, NEMESIS, NCS-R) half of all MDEs resolve rapidly in two to four months (Eaton et al., 1997, Spijker et al., 2002, Kessler et al., 2003) or even faster (Hämäläinen et al., 2008), but in about one fifth of all individuals with MDD, the course has been documented chronic (figure 3.)(Spijker et al., 2002). On the other hand, among incident cases of MDD in a twin study, Kendler found that 98% of episodes resolved within one year (Kendler et al., 1997).

Recurrences have been documented in about 40% of individuals followed up for decades after their first MDE (Mattisson et al., 2007); in retrospective analysis only a quarter reported no earlier MDEs in NCS-R (Kessler et al., 1997). In population samples longer time to remission or non-recovery have been consistently associated with higher severity of depression and longer duration, that is, the longer a person is ill, the lower his or her chances are of recovering (Keller, 1992).

4.6.3 Course and outcome of depressive disorders in primary health care

Though prognosis clearly serves the planning of treatment, in only few studies does the follow-up time exceed one year and only cross-sectional outcomes are reported. The course of depression has been followed with life-chart methodology in only one study in primary care; there the median duration of eight months was found in acute episodes of depressive disorders and 91% of MDE reached at least partial remission during 42 months follow-up (Oldehinkel et al., 2000). In cross-sectional outcome studies, full recovery in one year has been reported in a quarter to one-half of patients and chronic course in a third of patients (Ormel et al., 1993, Gaynes et al., 1999, Wagner et al., 2000, Lyness et al., 2002, van den Brink et al., 2002, Barkow et al., 2003, De Almeida Fleck et al., 2005)(Table 3). In MDD recurrent course has been suggested in one-half of patients in medium-term follow-up (Oldehinkel et al., 2000). Altogether, up to one-fifth of subsyndromal depressive symptoms seem to proceed to MDE in one year (Wagner et al., 2000, Lyness et al., 2002).

The clinical predictors of outcome in depressive disorders are not well known in primary care. In observational studies predictors of time to remission or recurrence have not been investigated. On cross-sectional outcome co-morbid Axis I disorders have had an adverse impact in many studies (Ormel et al., 1993, Gaynes et al., 1999, Burns et al., 2000, van den Brink et al., 2002, Barkow et al., 2003, De Almeida Fleck et al., 2005); among elderly, medical illnesses have served as a powerful predictor of the outcome (Lyness et al., 2002).

Table 3. Observational outcome studies in primary care with medium-term follow-up.

	Baseline					Follow-up		
Source	Major depression N /Subsyndromal depression N age range	Screening Diagnostic methods	Method of assessing severity of depression	Duration of episode/ recurrence assessed	Co-morbid Axis I/II/III disorders assessed	Months of follow-up Life-chart if used	Method of diagnosing outcome	Outcome
De Almeida Fleck et al., 2005	968/- 18-75	CES-D; acute and/or untreated depression CIDI	CES-D	-/Yes	I / - / III	9	CIDI and CES-D >16	Full remission 35% at 9 months
Barkow et al., 2003	725/- 18-65	GHQ-12 CIDI-PHC	Mild, moderate or severe depression	Yes/-	I / - / III	12	CIDI-PHC	Major depression 34% at 12 months
van den Brink et al., 2002	269/- 18-65	GHQ-12 CIDI-PHC	Number of depressive symptoms	Yes/Yes	I / - / III	12	CIDI-PHC	No recovery 29% at 12 months
Lyness et al., 2002	22/41 >59	CES-D SCID-I	HAM-D	-/-	- / - / III	12	SCID-I	Major depression 12% Subsyndromal depression 44% Full remission 43% at 12 months
Wagner et al., 2000	66/75 18-64	CES-D Telephone DIS	CES-D	-/-	I / - / III	12	Telephone DIS	Major depression 30% Subsyndromal depression 24% Full remission 46% at 12 months
Oldehinkel et al., 2000	54/32 17-65	30-GHQ; acute depression PSE	PSE score	Yes/-	- / - / -	42 and life-chart	PSE	At least partial remission from index episode 93% in median 8 months
Gaynes et al., 1999	85/- 18-64	CES-D Telephone DIS	CES-D	-/-	I / - / III	12	Telephone DIS	Major depression 44% Subsyndromal depression 25% Full remission 29% at 12 months
Ormel et al., 1993	52/27 17-65	30-GHQ; acute depression PSE	Major depression/ Subsyndromal deprression	-/-	I / - / -	42	PSE	Major depression 12% Subsyndromal depression 25% Full remission 63% at 42 months

4.6.4 Course and outcome of depressive disorders in psychiatric care

Compared to primary care, reports on course and outcome from psychiatric settings are abundant, and the overall picture of clinical depression has mostly been based on studies there.

Though achieving total remission in MDD has lasted a median of 11 months (Holma et al., 2008), already after 3 months (Furukawa et al., 2000) to 6 months (Keller, 1992) only some minor residual symptoms have existed. Residual symptoms are common (Melartin et al., 2005), especially after initially severe depression (Paykel et al., 1995), and they may persist for years (Judd et al., 1998) even with antidepressant treatment (Kennedy et al., 2004).

Moreover, a chronic course has been found in about one-tenth of patients (Holma et al., 2008a) or even in a higher percentage among inpatients (Keller, 1992). Poor prognosis has been consistently associated with longer duration or higher severity of depression and co-morbid dysthymia (Ramana, 1995, Parker, 2000, Solomon et al., 2000, Meyers et al., 2002, Melartin et al., 2004, Holma et al., 2008). Patients with current alcoholism in NIMH-CDS were only half as likely to recover from their MDE as those without (Mueller et al., 1994). Co-morbid chronic medical condition may in specialist care have only a minor effect on recovery from depression (Viinamäki et al., 2000).

A high number of recurrences of MDE have been documented in specialist care (Mueller et al., 1999, Viinamäki et al., 2002, Kennedy et al., 2003, Melartin et al., 2004, Holma et al., 2008). Approximately eight out of ten patients may experience more than one MDE during their lifetime (Mueller et al., 1999), the risk increasing hand in hand with the severity of depression (Ramana, 1995). Other reported risk factors of recurrences have been residual symptoms after recovery (Paykel et al., 1995, Judd et al., 1998), prior recurrences and relapses, long duration of current depression (Mueller et al., 1999) and co-morbid cluster C-personality disorders (Holma et al., 2008).

In specialist care, sociodemographic factors appear to have no significant effect on the outcome of MDD when depression severity and level of functional status are controlled for (Wells et al., 1992, Mueller, 1996).

4.7 Co-morbidity of depressive disorders

4.7.1 The concept of co-morbidity

Co-morbidity refers to the occurrence of two or more distinct disorders at the same time in an individual. Four main categories are apparent in co-morbidity (Robertson et al., 1997):

1) Coincidence of two illnesses, e.g when a psychiatric illness appears unrelated to a physical illness.

2) One disorder is a risk factor to another, e.g. depression may serve as an independent risk factor for ischemic heart disease in men (Hippisley-Cox et al., 1998).

3) Both illnesses have a common cause; either hereditary factors or environmental factors may have predisposed to both. E.g. generalized anxiety disorder (GAD) and MDD have shared genetic backgrounds but different environmental risk factors (Middeldorp et al., 2005).

4) One disease is the cause of another. Physical disease may cause psychiatric disorder either by biological or psychological mechanism. The difficulties in judging whether biological processes contribute to the aetiology of a psychiatric disorder has been recognized in DSM-IV; there "mood disorder due to general medical condition" include classification on the basis of the mood symptoms but with an extra code to indicate co-morbid physical illness (APA, 1994). [In the studies of this thesis, patients with mood disorders due to general medical conditions have been excluded.]

4.7.2 The mechanisms of co-morbidity in depression

The concept of co-morbidity has been introduced to psychiatry along the operational diagnostic system for mental disorders (APA, 1980). Co-morbidity of two or more psychiatric disorders has, however, been criticized for being an artefact produced by the categorical diagnoses, which are unable to differentiate disorders according to its pathogenesis or ethiology (Wittchen, 1996, Maj, 2005).

Growing evidence suggest that a vast majority of co-morbid depressive disorders occur secondary to other mental disorders, most often anxiety (Kessler et al., 1996, Wittchen et al., 2000). The presence of an anxiety disorder seems to be the single highest clinical risk factor for the development of depression (Wittchen et al., 2000). A common scenario appears to be the following: exposure to significant life stressors such as interpersonal conflict, some type of personal loss or some type of life threat leads to clinical levels of anxiety.Thereafter, the experience of anxiety may in turn serve as a compounding stressor that facilitates further decompensation, leading in patients, especially in those with genetic or familial diathesis, to MDD (Hirschfeld, 2001).

Within individuals with co-morbid depression and substance use, multiple pathways of association may act simultaneously. The combination of shared diathesis and causal models (in both directions) may explain why the association of depression with drugs or alcohol dependence does not show any unidirectional pattern (Swendsen et al., 2000).

The causal relationship between personality disorders and MDD is unclear; two commonly proposed explanations are the "vulnerability" model, where certain personality traits serve as risk factors for the development for depression (Shea et al., 1996) and the "scar" model suggesting that a depressive episode is the cause of a permanent change in the personality.

Among elderly primary care patients, medical illnesses serve as a frequent precipitant of depressive conditions (Lyness et al., 2002). A hypothesis has suggested that the association may be either multimodal or involve a final common pathway that includes elements common to many diseases, e.g. the potential role of inflammatory cytokines, or common psychosocial factors or altered social-role functioning (Lyness et al., 2002).

4.7.3 Methodological aspects in research on co-morbidity

Depressive disorders seldom present in pure forms even in population samples (Kessler et al., 2003). Across studies there is, however, in the magnitude of co-morbidity substantial variation at least partly due to methodological incompatibilities in terms diagnostic assessments, timing of diagnosing, time frame (e.g. lifetime or current), and health care settings (Wittchen, 1996) to mention a few.

Moreover, the significance of co-morbidity in the clinical picture, course and outcome of depression often remains unclear. The effect of overall co-morbidity on the length of episode or risk of recurrence has rarely been systematically investigated (Melartin et al., 2002), and available studies mainly focus on a single type of co-morbid disorder. Most studies have not used semistructured or structured interviews for both MDD and co-morbid disorders, controlled for the effects of additional co-morbid disorders nor used life-chart methodology, but rather only report cross-sectional findings.

4.7.4 Psychiatric co-morbidity of depressive disorders in population samples

Bearing in mind the methodological limitations, population surveys suggest that co-morbidity in MDD is more a rule than an exception. In NCS-R only one-fifth of individuals with 12-month MDD did not have a 12-month Axis I co-morbid DSM-IV disorder; 58% had anxiety disorder and 9% had substance use disorder (Kessler et al., 2003). In Finland, a third with anxiety disorder and a tenth with alchohol use disorder were found (Pirkola et al., 2005c). In NESARC, at least one personality disorder was present in 46% of individuals with 12-month MDD, most often obsessive-compulsive or paranoid personality disorder; among those with dysthymia, personality disorders were even more prevalent (55%)

(Grant et al., 2005). In the Zurich Cohort Study among individuals with current subsyndromal depressions, a third suffered from a diagnostic or subthreshold anxiety disorder (Preisig et al., 2001).

4.7.5 Psychiatric co-morbidity of depressive disorders in primary care patients

Among primary care patients with MDD, psychiatric co-morbidity is highly prevalent. In the WHO PPGHC study, 62% of the patients with current MDD also had another psychiatric diagnosis (Wittchen et al., 1999). For co-morbid anxiety disorders, prevalence rates of 23% to 50 % have been reported (Coyne et al., 1994, Sartorius et al., 1996, Sherbourne et al., 1996, Gaynes et al., 1999, Lenze et al., 2000), and for co-morbid substance use disorders, from 6% to 33% (Coyne et al., 1994, Roeloffs et al., 2001). The prevalence of Axis II co-morbid disorders has only been reported from a few treatment intervention studies, which are unlikely to be representative of patient populations in primary care (Patience et al., 1995, Brown et al., 1996, Ekselius et al., 1998). Among primary care patients with subsyndromal depressive disorders a third may have psychiatric co-morbidity: anxiety disorders have been found in 16% (Coyne et al., 1994) and substance use disorder in 9% (Olfson et al., 1996).

4.7.6 Psychiatric co-morbidity of depressive disorders in psychiatric patients

The majority of research on co-morbidity in MDD has been conducted in psychiatric settings. The full Axis I and Axis II repertoire has been investigated among patients in secondary level psychiatric care in the Vantaa Depression Study (VDS); the reported prevalences of current co-morbid anxiety disorders were 57%, substance use disorders 25%, and, personality disorders 44% (Melartin et al., 2002). The co-morbidity tended to cluster in the same patients. In patients with subthreshold depression, the overall co-morbidity has been reported similar to those with MDD except for a smaller amount of anxiety disorders (Sherbourne et al., 1994).

4.7.7 Medical co-morbidity of depressive disorders

A bidirectional relationship has been observed between depression and medical illnesses: compared to the general population those with chronic illnesses often have much more co-morbid depression (Cassem, 1995). Depression also serves as an independent risk factor for some medical illnesses, such as cardiovascular disease, epilepsy and stroke (Hippisley-Cox et al., 1998, Evans et al., 2003). Furthermore, depression may promote adverse health behaviours such as smoking, unhealthy diet, sedentary lifestyle and poor adherence to medical regimens (Katon, 2003) which may serve as risk factors for medical illnesses.

In the WHO PPGHC study, the risk of co-morbid medical illness was 2.5 times higher in patients with MDD than in non-depressed patients; e.g. observed coexistence of coronary heart disease and depression has been higher than expected by chance (Maier et al., 1999).

The prevalence of chronic somatic diseases in patients with MDD has been found between 60% and 80% (Coulehan et al., 1990b, a, Koike et al., 2002). Moreover, in patients with MDD physical illnesses have appeared more severe than in non-depressed patients (Coulehan et al., 1990b) as well as, in them, complaints of disabling pain have appeared more frequent (Arnow et al., 2006).

In IMPACT study, elderly patients with MDD or dysthymia had about four co-morbid chronic somatic illnesses each (Harpole et al., 2005); depression, however, had the most impact on their well-being (Ormel et al., 1998).

4.7.8 The impact of co-morbidity of depressive disorders

In the research on co-morbidity in depression, most attention has been given to anxiety disorders. Besides the adverse impact on course and outcome, it has been shown to increase the severity of depression and cause greater impairment in work functioning, psychosocial functioning and quality of life than in patients without co-morbid anxiety (Brown et al., 1996, Olfson et al., 1997, Kessler et al., 1998, Roy-Byrne et al., 2000). Moreover, co-morbid anxiety has been shown to significantly increase the suicide attempt risk above what is contributed by MDD alone (Kessler et al., 1998); rates of suicide attempt are suggested to be 70% higher in patients with co-morbid MDD and panic disorder than in those with MDD alone (Roy-Byrne et al., 2000). On the other hand, the coexistence of anxiety disorder with depression seems to enhance help-seeking (Roy-Byrne et al., 2000).

Co-morbid physical illnesses influence on presentation and recognition of depression in primary care thus forming a barrier against adequate care (Simon et al., 1999b). Moreover, concurrent physical symptoms appear to influence on severity and symptom patterns of MDD (Yates et al., 2004).

According to natural and treatment studies of depressed patients with and without arthritis, chronic obstructive pulmonary disease, diabetes or heart disease, depression significantly increases the functional impairment in medical illness (Simon, 2003) and contributes to the economic burden of the medical illness; medical costs for patients with MDD are approximately 50% higher than the costs of chronic medical illness alone (Simon, 2003).

Treatment guidelines suggest co-morbidity patterns taken into account in the choice of treatment modality (AHCPR, 2000). The overall impact of co-morbidity on treatment response remains however, obscure, as various types of co-morbidity may have a very different impact. The effect of co-morbid psychiatric disorders on treatment response in intervention studies varies. According to some studies, neither co-morbid anxiety disorders nor personality disorders had any major effects on treatment responses in psychiatric care (Mulder, 2002, Krishnan, 2003), whereas concurrent medical illness predicted worse treatment outcome in depression in another study (Iosifescu et al., 2003). In primary care interventions co-morbidity has associated with poorer treatment response

(Brown et al., 1996), on the other hand, e.g. IMPACT study has shown that elderly individuals with medical co-morbidity seem to respond to treatment similarly to those without any medical co-morbidity (Harpole et al., 2005).

Overall, co-morbidity of another disorder in depressive disorders quite constantly seems to cause more functional impairment, higher economical costs in health care and higher utilization of medical services (Sherbourne et al., 1996, Hirschfeld, 2001, Rytsälä et al., 2006).

4.8 Suicidal behaviour

4.8.1 Classification of suicidal behaviour

The concept of suicidal behaviour ranges from suicidal ideation to suicide attempts and completed suicide and it may vary with respect to manifestation, performance, seriousness and lethality (Beck, 1986).

Suicidal ideation is usually defined as thoughts and wishes of suicide in individuals who have not made any overt suicide attempts (Beck, 1986). Suicidal ideation includes suicide threats, suicidal preoccupations and expressions of the wish to die as well as indirect indicators of suicide planning. Suicidal ideation appears to be an important marker for identifying patients at risk of suicide (Brown et al., 2005).

Suicide attempt is defined by APA as a self-injurious behaviour with a non-fatal outcome accompanied by evidence (either explicit or implicit) that the person intended to die (APA, 2003), where intent is defined as subjective expectation and desire for a self-destructive act to end in death (APA, 2003). Suicide attempt may be replaced by other terms in research literature, such as deliberate self-harm which in the U.K. is used for all episodes of survived self-harming behaviours regardless of intent. In North America deliberate self-harm usually refers to repetitive suicidal behaviour (Skegg, 2005), but not for overdoses or if methods of high lethality have been used.

Suicide is defined as a self-inflicted death with evidence (either explicit or implicit) that the person intended to die (APA, 2003).

4.8.2 Stress-diathesis model

Suicidal behaviour usually presents with a psychiatric disorder. While most psychiatric patients never attempt suicide, additional risk factors are, however, required. To better explain the process and risk for suicidal behaviour a stress-diathesis model has been proposed (Mann, 2002). The diathesis in the model is understood as a predisposition which may affect the threshold for suicidal behaviour when a stressor is present. The diathesis consists of enduring conditions or traits such as hopelessness and increased lifetime

impulsivity that may be related to specific impairment of serotonergic input into the ventral prefrontal cortex (Mann et al., 1999). Among the many types of triggering stressors, the onset or acute worsening of psychiatric disorder is nearly always present in suicide attempters (Mann, 2002). In the model, at least one major risk factor from both stressors and diathesis must be present to form high risk for suicide (Mann, 2002).

4.8.3 Epidemiology and risk factors of suicidal ideation

Suicidal thoughts are common; approximately 11-18% in population samples across Western countries report having experienced suicidal ideation at some point during their life (Weissman et al., 1999), but worldwide, huge differences exist in reported prevalence rates across countries: from 3% to 25% of population have experienced suicidal ideation and from 1% to 16% have made suicide plans (Weissman et al., 1999, Bertolote et al., 2005, Bernal et al., 2007). Some of the differences across the sites are most probably affected, beside the various ways of asking about suicidal ideation, by the differences in the willingness of respondents from different cultures to report suicidal thoughts (Bertolote et al., 2005).

In U.S., large population surveys (NCS, NCS-R) report 12-month prevalence of suicidal ideation to be around 3 % and of suicide plans to be around 1% (Kessler et al., 2005a). In Slovenia, a country of high suicide mortality (Schmidtke, 1997), 22% of the general population acknowledge having had suicide thoughts during the last year (Kocmur et al., 2003). In the Finnish study the 12-month prevalence was 15% - contrary to most other countries, in Finland the prevalence was higher in men than in women (Hintikka et al., 2001).

Suicidal thoughts in clinical patient samples are more frequent than in the general population. Even in primary care, persons with suicidal thoughts are many times more likely to visit their care doctor than those without suicidal thoughts (Goldney et al., 2001). Suicidal ideation could be obtained in about 9% of unselected primary care patients in a self-report questionnaire (Goodwin et al., 2003). In Australia, 6 % of elderly primary care patients acknowledged current suicidal ideation (Pfaff et al., 2006). However, about half of individuals experiencing suicidal thoughts do not perceive the need for care, and of those who do, many experience difficulties in obtaining it (Brook et al., 2006).

The most consistently identified risk factors of suicidal ideation have been depression and hopelessness (Hintikka et al., 2001, Casey et al., 2006). Moreover, suicidal ideation has been related to younger age, female gender and a low level of education (Kessler et al., 2005a, Bernal et al., 2007). Protective factors have been getting older and having meaningful social relations (Casey et al., 2006).

4.8.4 Suicidal ideation in patients with depressive disorder

While depression is a major risk factor for suicidal ideation, it is not unexpected that among patients with MDD, more than a half in psychiatric settings (Sokero et al., 2003) and a third in primary care have reported suicidal ideation (Ahrens et al., 2000). In a thorough Finnish study, independent risk factors have been hopelessness, alcohol problems, low level of social and occupational functioning and poor received social support among psychiatric in- and outpatients with MDD (Sokero et al., 2003). Other reported risk factors consist of severe depression, and co-morbid dysthymia, anxiety and personality disorders (Van Gastel et al., 1997, Hintikka et al., 1998, Alexopoulos et al., 1999, Schaffer et al., 2000), as well as female gender, younger age and severe adverse life events (Schaffer et al., 2000, Monroe et al., 2001, Casey et al., 2006). Previous suicide attempts also predict suicidal ideation (Alexopoulos et al., 1999).

4.8.5 Epidemiology and risk factors of suicide attempt

Official suicide attempt rates are not available in most countries. The WHO/EURO Multicentre Project on Parasuicide has gathered comparable information in 13 European countries in 1989-1992: the highest rate of suicide attempts among males was in Finland and the lowest in Spain, representing a 7-fold difference (Schmidtke et al., 1996). Around the world even higher variation across nations has been reported (from 0.4% to 4.2%) (Bertolote et al., 2005). A part of the variation may be explained by different cultural attitudes towards suicidal behaviour and by the willingness to report suicide attempts (Schmidtke et al., 1996). There are indications that, depending on the site, the ratios between attempts, plans and thoughts of suicide differ substantially and that the burden of undetected attempted suicide is high in many cultures (Bertolote et al., 2005).

In the WHO/EURO Multicentre Project on Parasuicide more than half of the suicide attempters made more than one attempt, it has been reported that nearly 20% of the second attempts were made within 12 months of the first attempt (Schmidtke et al., 1996). Nearly all suicide attempters have suffered from one or more psychiatric disorder (Suominen et al., 1996, Kessler et al., 2005a). In WHO/EURO Multicentre Project on Parasuicide, with only one exception (Helsinki), suicide attempt rates were higher among women than men. In the majority of centres, the highest rates were found in the younger age groups. Risk for suicide attempts has also been related to being divorced or widowed, and to low educational level (Kessler et al., 1999b).

Though nearly 2% of those who harm themselves may die within the following year by suicide (Owens et al., 2002), the aftercare in medical emergency units appear varying and insufficient (Kapur et al., 1999): only about half of suicide attempters have received psychosocial assessment and in most studies only few get admission to psychiatric services (Kapur et al., 1999, Suominen et al., 2004b). In a Finnish study, half of young suicide attempters failed to have any health care contact in the month following the visit at the

emergency unit (Suominen et al., 2004b), while most elderly suicide attempters, however, were referred for aftercare mainly to psychiatric services (Suominen et al., 2004a). Furthermore, in a study by Haw, where the majority of patients were offered treatment in psychiatric services, only a minority stayed in contact (Haw et al., 2002). Also most suicide attempters have not communicated their suicidal thoughts, even though the majority have had recent contact with medical services (Houston et al., 2003).

4.8.6 Suicide attempts in patients with depressive disorders

A suicide attempt, especially if followed by death, is the most important complication of depression. Of individuals with a lifetime diagnosis of MDD, 16% acknowledged having attempted suicide at some point in their lifetime in ECA survey (Chen et al., 1996); the first suicide attempt seems to occur within 5 years from the onset of MDD in 40% of patients with depression (Malone et al., 1995a). One quarter may repeat the attempt within a year (Bradvik, 2003).

Independent predictors, reported by Sokero et al. (2003), for suicide attempts among psychiatric in- and outpatients with DSM-IV MDD are severity of depression and alcohol dependence or abuse in particular; also younger age and a low level of social and occupational functioning were risk factors (Sokero et al., 2003).

Others may be hopelessness, impulsiveness (Maser et al., 2002), co-morbid personality disorder (Hawton et al., 2003), recent adverse life events and marital problems (Malone et al., 1995a, Oquendo et al., 2006). A prior suicide attempt serves as a significant indicator of risk (Oquendo et al., 2006). In clinical risk factors there appears to be some gender related differences (Oquendo et al., 2007): e.g. in women the importance of past suicidal behaviour is higher, each past suicide attempt increases the future risk threefold (Oquendo et al., 2007).

Despite its clinical importance, not all depressed patients at the time of the suicide attempt are receiving treatment or adequate pharmacotherapy (Oquendo et al., 2002). Haw et al. (2002) found that one third of attempters were receiving treatment for depression in psychiatric services and another in primary care (Haw et al., 2002). In a Finnish study the majority of elderly suicide attempters had had recent contact with primary care, but their mood disorders had often remained undiagnosed before the attempt (Suominen et al., 2004a). Even in psychiatric hospitals a fourth of clinicians may fail to document the history of suicidal behaviour in patients with MDD and past suicidal attempts (Malone et al., 1995b).

4.8.7 Epidemiology of suicide

Suicide is an important course of mortality accounting for 887 000 deaths every year (WHO 2003). Rates of suicides vary greatly across countries (Schmidtke, 1997), at least partly due to transcultural differences in age structure and socioeconomic factors, the influence of race and ethnicity and the impact of religion, to mention a few (De Leo, 2002, Oquendo et al., 2004).

The official rates depend, moreover, on legislation of suicide, the death certification procedures (Schmidtke et al., 1996) and prevalence of undetermined deaths (Marusic et al., 2003). Everywhere in the world, suicide rates among males are manifold higher than in female for all age groups (Schmidtke et al., 1996). The Finnish suicide rate is among the highest in Europe (altogether 1062 in 2006) (Tilastokeskus, 2008).

4.8.8 Risk factors of suicide

What drives individuals to take their own life remains unanswered despite numerous studies. The major obstacle to an understanding of suicide is that the victim cannot be interviewed and the reason directly ascertained. Psychological autopsy is probably the most direct technique for determining the relationship between particular risk factors and suicide (Isometsä, 2001, Cavanagh et al., 2003).

Psychiatric disorders, present in nine out of ten suicide victims (Arsenault-Lapierre et al., 2004), are the most significant predictors of suicide risk (Cavanagh et al., 2003) especially when necessitating hospital admission (Bostwick et al., 2000, Mortensen et al., 2000, Pirkola et al., 2005b). Particularly vulnerable periods seem to occur during admission and soon after discharge (Mortensen et al., 2000). In the majority of suicides more than one psychiatric illness has been present, most frequently affective disorders especially among women and substance use disorders in men (Cheng et al., 2000, Cavanagh et al., 2003, Arsenault-Lapierre et al., 2004) (Henriksson et al., 1993, Mann et al., 2006).

Medical illnesses increase the risk for suicide (Koponen et al., 2007) especially in the elderly and in patients suffering from disorders of the central nervous system (Breslau et al., 1991). In other potentially fatal illnesses, such as cancer, the increase in risk is only modest unless a combined psychiatric disorder is present (Henriksson et al., 1995).

Hopelessness, defined as a state of negative expectations, is an important psychological variable of suicidal behaviour which is believed to mediate the association between depression and suicidal behaviour (Beck et al., 1993). Whether it leads to suicidal behaviour depends upon the presence or absence of risk and protective factors (Beck et al., 1993).

Psychosocial and other environmental factors influencing on the risk of suicidal death are male gender, advancing age (Hawton et al., 2003), lack of social network, recent adverse life events and socioeconomic difficulties (Cheng et al., 2000, Suokas et al., 2001). Other suggested risk factors of suicide are *availability of lethal methods* such as domestic coal gas, barbiturates and firearms (Oliver et al., 1972, Kreitman, 1976, Wintemute, 1988), and *suicide stories of high publicity* (Hassan, 1995).

A family history of suicide has been shown to increase the the risk for suicide in other family members (Brent et al., 1996, Cheng et al., 2000).

Past suicidal behaviour, both ideation and attempts, are strong risk indicators for future suicide (Brown et al., 2000). Within the year following a suicide attempt, the risk of eventual death by suicide is about 100 times greater than that of the general population (Hawton, 1987). Suicides seem to accumulate even years after an attempt (Suominen et al., 2004c). It has been postulated that a lifetime history of suicide attempts can lower the threshold of new attempts and thus suicide related structures may become more easily triggered (Joiner et al., 2000). It has to be remembered, however, that over half of suicide victims die at their first suicide attempt, according to Isometsä and Lönnqvist (1998), and thus even if a suicide attempt is a powerful single predictor of completed suicide, its sensitivity as a risk factor is limited (Isometsä et al., 1998).

4.8.9 Depressive disorders and completed suicide

A highly quoted meta-analysis of Guze & Robins (1970) suggested that 15% of psychiatric patients with severe affective disorders will die of a suicide (Guze et al., 1970). Thereafter this high figure has been uncritically generalized to concern all depressive disorders and not until lately been debated and reassessed.

Bostwick & Pankratz (2000) have demonstrated a hierarchy of risk based on the intensity of the treatment setting; they found a lifetime risk of 4.0% for suicide in their meta-analysis for affective disorder patients hospitalized without specification of suicidality (Bostwick et al., 2000). Furthermore, suicide mortality among depressed patients in primary care has been shown to be much lower than in psychiatric settings (Simon et al., 1998).

In patients with depression the risk factors for completed suicide tend to overlap the general risk factors for suicide. They include male gender (Hoyer et al., 2004), hopelessness (Coryell et al., 2005) and adverse life events (Mann et al., 2005b). Co-morbid psychiatric disorders have often been present, such as substance use disorder and personality disorder (Dumais et al., 2005, Gonda et al., 2007, Oquendo et al., 2007). Especially in depressive men, impulsive-aggressive personality and alcohol disorders may be independent risk factors (Dumais et al., 2005). In depressed patients prior suicidal behaviour (Oquendo et al., 2006) and previous psychiatric hospitalizations also indicate

risk of suicides. In non-psychiatric patients with depression the suicidal intent has usually not been communicated to health care professionals and the depression has remained untreated (Isometsä et al., 1995).

4.8.10 Prevention of suicidal behaviour

Given the rarity of completed suicides even in highrisk populations, many individuals need to be targeted in order to prevent few suicides. To address the multiple causes of suicidal behaviour, prevention strategies usually involve a multifaceted approach with particular attention to mental health.

Primary prevention of suicide requires focusing on preventive measures or protective factors such as restricting access to lethal methods (firearms, pesticides, toxic gas, barbiturates etc.), which is a major component of current international suicide prevention strategies (WHO), the toning down of reporting of suicides in the media and public education campaigns to increase knowledge on mental illness and suicide (Mann et al., 2005a).

Secondary prevention options include early detection of suicidal individuals as well as accurate diagnosis and effective treatment of psychiatric disorders - another major component of international prevention strategies (WHO). While more than half of those who die by suicide had recently contacted a primary care doctor (Luoma et al., 2002) detection of their suicidal intent might have been possible in some cases.

Despite their importance for planning, the relative impact of various strategies on national suicide rates has been difficult to estimate. In a recent systematic review (Mann et al., 2005a) physician education, means restriction and gatekeeper education have been the most promising interventions. Public education campaigns have increased knowledge and improved attitudes toward mental illness and suicide, but measures for suicide prevention have been insufficient (Mann et al., 2005a).

Studies examining suicidal behaviour in response to primary care physician education programs, mostly targeting depression recognition and treatment in limited regions in Sweden, Hungary, and Japan (Rihmer et al., 1995, Oyama et al., 2006, Szanto et al., 2007), have all reported an increased prescription rate of antidepressants and often a decline in suicide rates.

Despite the huge burden caused by suicide mortality, the number of national policies for preventing suicides is low; Finland published, the first country worldwide, a national strategy of suicide prevention and an action plan for implementation in 1991. It was a part of the National Suicide Prevention Project, which was carried out from 1986 to 1996. The aim was to stop the increasing trend and decrease suicide mortality by 20% by the year 1995. During the first years the number of suicides increased, followed by a reduction of 20% between 1991 and 1996, since then the suicide rate has decreased steadily and the

annual amount of suicides has declined to below 1000 (Lönnqvist, 2007). However, Finland still has a relatively high suicide rate compared with other Western EU countries (Schmidtke, 1997), suicide being the leading cause of death in Finland among those under the age of 35 years (Tilastokeskus, 2008).

4.9 Treatment process in primary care

4.9.1 The pathways to care

Goldberg and Huxley have suggested a framework for understanding the pathways by which individuals become defined as mentally ill and by which they eventually reach a mental health specialist (Goldberg et al., 1980). They introduced five levels (1) community, 2) primary care with total load of mental illness, 3) primary care with detected mental illnesses, 4) specialist mental health services, and 5) inpatients) and four "filters" through which patients have to pass to reach the next level. The first filter consists of a person's interpretation of signs of distress (either physical or psychological) as an illness. Guided by this interpretation the person may seek help by consulting a primary care doctor and thus move to the next level. The second and third filters in primary care concern detection, diagnostics and referral. The fourth filter in specialist services concerns admission.

Passing the first filter, with any presenting complaints either somatic or psychosocial, provides the primary care level with opportunities to promote health and prevent disease (Üstün, 2000). The second filter, however, has to be passed in order to receive treatment for depression. The permeability of the third filter reflects the allocation of resources and responsibilities in the particular health care system and the fourth filter concerns allocation of responsibilities within specialist care.

For a better understanding on the pathways to care, multiple factors influencing in all the levels introduced by Goldberg have to be considered, such as barriers in help-seeking in the public, the ways of reaching the diagnosis of depression in primary care, the possibilities of following practice guidelines among doctors and compliance in patients, and finally, the rules in allocating resources and responsibilities within and between the health care providers.

4.9.2 Help-seeking behaviour

Only a minority of primary care patients with depressive disorders have sought treatment for depression. A major obstacle in primary care studies has appeared to be stigma (Cooper-Patrick et al., 1997, Docherty, 1997), that is the negative stereotyping related to persons with mental illnesses (Link et al., 2006). Furthermore, the decision to seek help is influenced by expectations regarding the care (Cooper-Patrick et al., 1997), attitudes towards professional help and beliefs about the helpfulness of different types of treatment (Fortney et al., 1998). More than one third of primary care patients with depression seem to be reluctant to accept the diagnosis (Williams et al., 1999).

4.9.3 Recognition of depressive disorders in primary care

Primary care doctors often have a difficult task, from several presenting problems and clues, to distinguish symptoms of psychological origins (Klinkman, 1997). About half of all depressive disorders are overlooked at a consultation (Coyne et al., 1995); at subsequent visits, however, the rate of recognition increases modestly (Kessler et al., 1999a).

Various patient-, doctor- and provider-related factors may influence the possibility of depression remaining unrecognized. Patients may not realize the need for treatment (Tylee et al., 2007) or they do not want it (Olfson, 1991a). Though the majority of patients with depression present with physical symptoms (Simon et al., 1999b), particular complaints, such as sleep disturbances, non-specific musculoskeletal pains, back pain, shortness of breath, or amplified and multiple or vaguely stated complaints, have appeared to distinguish depressed patients from non-depressed primary care patients (Gerber et al., 1992).

Increasing the "hit rate" of recognition is an option, as the majority of individuals with untreated depression consult their primary care doctors on other health questions (Tiemens et al., 1996, Bebbington et al., 1997). The diagnosis of depression may, however, be missed due to multiple doctor-related causes such as the doctors' negative attitude towards mental health problems, the doctors not feeling responsible for dealing with them (Main et al., 1993, Robbins et al., 1994) or their lack of communication skills (Goldberg et al., 1993). Primary care doctors appear, however, to respond to meaningful clinical clues in assigning the diagnosis of depression such as distress, severe symptoms of depression, co-morbid anxiety or history of treatment for depression (Coyne et al., 1995, Schwenk et al., 1996, Klinkman et al., 1998, Wittchen et al., 2001). Particularly depression with moderate or severe disability has been consistently recognized in studies across centres (Ormel et al., 1994, Von Korff et al., 1996b). On the other hand, depression is particularly likely to be overlooked in patients with true physical illness (Coulehan et al., 1990b) and in those who present with somatic complaints (Gerber et al., 1992, Kirmayer et al., 1993). The recording of the depression diagnosis in the medical

records is less likely to happen during visits made by elderly patients and on shorter visits (Harman et al., 2001). Overall, attempts to influence clinician behaviour through a process of adaptation and extension of guidelines have not succeeded in changing detection rates (Croudace et al., 2003).

According to the WHO PPGHC study, the recognition of depression was considerably better in centres with a client-centred care model: personal doctor, no or short waiting time, medical records kept on all patients seen and physicians responsible for aftercare of illnesses. Even in client-centred practices the primary care doctors may, however, lack time and facilities, when bureaucratic complexity increases their workload in poorly organized practices (Mechanic, 2001).

4.9.4 The consequences of unrecognition

While the recognition in primary care is more probable in more severe and disabled patients (Coyne et al., 1995), it has been suggested that the consequences of missing the diagnosis might not have great clinical importance (Goldberg et al., 1998). Only short-term, but not long-term, improvement in outcome has been reported in relation to recognition and appropriate diagnosis (Goldberg et al., 1998, Simon et al., 1999a). Overall, the poor prognosis among patients with both undetected depression (Rost et al., 1998) and detected depression suggests that improving the "hit rate" is only a first step toward more appropriate treatment (Goldberg et al., 1998, Simon et al., 1999a). Besides the primary care doctor must be offered the resources to deal with the cases they discover (Tiemens et al., 1996).

4.9.5 Screening for depressive disorders

Screening seems to improve the accuracy of identifying depression (Pignone et al., 2002). For screening, a number of useful and accurate tools are available (Williams et al., 2002), such as Beck's Depression Inventory (BDI) (Beck et al., 1961) and Depression Scale (DEPS) (Salokangas et al., 1995); even two verbally asked questions concerning lowered mood and anhedonia seem to detect most cases of depression in primary care (Arroll et al., 2003).

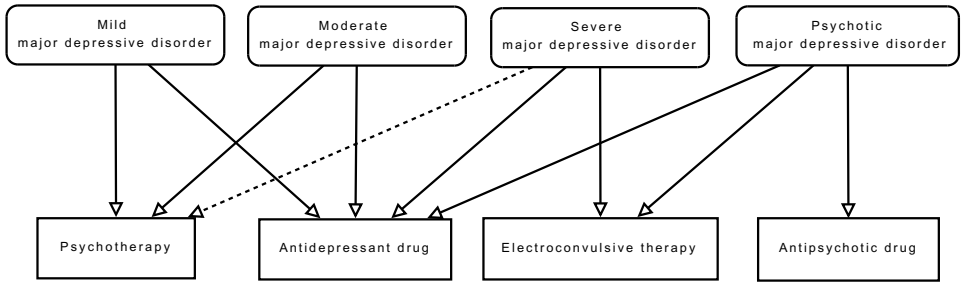
Screening alone, however, is unlikely to be a clinically or cost-effective way to improve the mental well-being of the population (Gilbody et al., 2006), but as a part of an integrated management system, evidence exists of improvement in patient outcome (Pignone et al., 2002, Bijl et al., 2004). The available positive evidence led the U.S. Preventive Services Task Force (USPSTF) to recommend that adults be screened for depression "in clinical practices that have system in place to assure accurate diagnosis, effective treatment, and follow-up" (Pignone et al., 2002). In England, as well as in Finland, screening has been supported more cautiously. The National Institute for Health and Clinical Excellence (NICE) recommends that it should be offered to people at high risk of depression (NICE, 2004), such as patients with diabetes (Isometsä et al., 2003, Katon et al., 2004b).

Although the optimal interval for screening is unknown, the U.S. task force stated "recurrent screening may be most productive in patients with past history of depression, unexplained somatic symptoms, co-morbid psychological conditions, substance abuse, or chronic pain" (Pignone et al., 2002). In cost-utility analysis one-time screening appears cost-effective; Moreover, cost-effectiveness is likely to improve if treatment becomes more effective (Valenstein et al., 2001).

4.9.6 Treatment guidelines for depressive disorders

Several sets of evidence-based practice guidelines have been published in order to improve treatment of depression (Cohen et al., 1997, Ellis et al., 2002, Isometsä et al., 2003, Bech, 2004, NICE, 2004, Goldberg, 2006). There exists some variation in the recommendations; the main treatment modalities in all of them, however, consist of pharmacotherapy, psychotherapy and electroconvulsive therapy (figure 4.).

Figure 4. Treatment guidelines for acute Major Depressive Disorder in the national Finnish current care guidelines for the treatment of depression (Isometsä et al., 2003).



Treatment trials in primary care settings have shown that the efficacy of antidepressants as well as psychotherapy in the treatment of MDD transfers from specialist care to primary care (Schulberg et al., 1998). Of them, antidepressive medication is probably the far most offered treatment modality in primary care. There is strong evidence that antidepressants are effective in treatment of dysthymia as well, despite the limited amount of long-term documentation (Bech, 2004).

Increasing evidence supports the use of a specific psychotherapy in the continuation and maintenance phases to prevent recurrences (AHCPR, 2000, Isometsä et al., 2003). Clinical features that may suggest the use of psychotherapeutic intervention (cognitive, behavioural, interpersonal, psychodynamic) include the presence of psychosocial stressors; concerning intrapsychic conflict, interpersonal difficulties, or co-morbid Axis II

disorders; especially in moderate to severe MDD, psychotherapy may be combined with medication (AHCPR, 2000). Poor adherence to treatments may also warrant a combination of treatment modalities (AHCPR, 2000). In a recent systemic review, Pampallona et al. (2004) concluded that combined antidepressant therapy and psychosocial treatment is associated with a higher improvement rate than pharmacotherapy alone (Pampallona et al., 2004). Furthermore, guidelines suggest that treatment should aim at full recovery i.e. the patient is symptom free and able to function well socially and at work (Bech, 2004).

A number of studies based on these guidelines have demonstrated significant improvements in outcomes when the implementation of guidelines was accompanied by active care management and patient education (Williams et al., 2007).

4.9.7 Treatment of depressive disorders in patients with medical illness

The factors needing special consideration in the treatment of MDD in patients with medical illnesses are drug interactions and the potential exacerbations of medical symptoms caused by antidepressants (Ellis et al., 2002). Considering the extent to which depression presents in chronic medical illnesses, surprisingly, only a half of the 150 available practice guidelines for general medical conditions have mentioned depression treatment at all; the majority of these only addressed depression screening. Only three addressed modifications to the general medical strategy in patients with co-morbid MDD (Kilbourne et al., 2006). In general, Cochrane Collaboration has concluded that antidepressants improved MDD outcome in patients with a range of physical diseases, with an overall Number Needed to Treat (NNT) of 4.2 (Gill et al., 2007).

4.9.8 Shortcomings in treatment of depression

Despite the key role of primary care in the treatment of depression its quality remains far from optimal there (Wittchen et al., 2001, Young et al., 2001): drug treatment continues to be inadequate in dosage, duration, or both, and only to a small minority are psychotherapeutic visits offered (Katon et al., 2004a). Moreover, patients are referred to non-directive counselling, which has not shown to be effective for the treatment of depression (Friedli et al., 1997).

Various doctor-, patient-, and provider-related factors may influence on the quality of treatment. Patient attitudes and beliefs, according to primary care doctors, are primary impediments to implementing guideline concordant care (Nutting et al., 2002). Patients are reluctant to take drugs for depression (Priest et al., 1996), and only 30% to 60% of them take their medication as prescribed (Dunn et al., 1999). The lack of availability of adequately trained psychotherapists is another obstacle (Ebmeier et al., 2006), although many patients prefer psychotherapy to usual care (Friedli et al., 1997).

Although following treatment guidelines is known to improve outcome, primary care doctors frequently miss the recommendations, especially in management of suicide risk, co-morbid

alcohol problems and elderly patients, as well as in assessment of history and symptoms of depression and treatment adjustment for patients who do not respond to initial treatment (Hepner et al., 2007).

Psychiatrists and other mental health professionals are not accessible to many depressive patients. Furthermore, health care systems often fail to organize mental health consultation services to support the work of primary care physicians who treat their depressive patients (Pincus, 2006).

4.9.9 Management of patients with depression in primary care

Despite the potential in primary care for a long-term and integrative perspective, depression there remains a condition with suboptimal management. A number of educational strategies targeted at health care professionals as well as new methods of organizing and providing care have been proposed for its improvement (Cabana et al., 2002). Wagner has designed chronic care models to provide the best possible functional and clinical outcomes by optimizing the interaction between an effective practice team and the active patients (Wagner et al., 2001). For these interactions to take place, an infrastructure needs to support them. The effectiveness of these models is supported by results of multiple projects, such as Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) (Unutzer et al., 2002) and Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) (Wells et al., 2000). In a systematic review, improvement in the patient outcome was achieved in multifaceted strategies, where clinician education, enhanced role of nurse case manager and a greater degree of integration between primary and secondary care were incorporated (Gilbody et al., 2003). Examples of such strategies have been Collaborative Care (Katon et al., 1995) and Stepped Collaborative Care strategies (Katon et al., 1999) and IMPACT (Unutzer et al., 2002). Telephone medication counselling delivered by a practice nurse was effective as well (Simon et al., 2000). Beside improved quality of depression care, such disease management programs have increased patient and provider satisfaction (Badamgarav et al., 2003, Gensichen et al., 2005), and may successfully be implemented in a wide range of primary care settings and geographic sites, serving diverse ethnic and socioeconomic groups with promising results (Dietrich et al., 2004) and with only modestly increased overall costs of care (Neumeyer-Gromen et al., 2004). Moreover, simple guideline implementation and educational strategies have been generally ineffective, such as the large educational program in Hampshire Depression Project, which failed to improve outcome for patients (Thompson et al., 2000).

4.9.10 Referral to mental health services

The majority of patients who receive specialist psychiatric care have entered the services via primary care (Gater et al., 1991). Referral to psychiatric care in various national practice guidelines is recommended for patients with psychotic depression and at a high risk of suicide, and less consistently, for other patient groups with characteristics related to poor prognosis such as illness severity, co-morbid personality disorder and non-succesful treatment by the primary care doctor (Cohen et al., 1997, Ellis et al., 2002, Isometsä et al., 2003, Bech, 2004, Goldberg, 2006).

When choosing the service provider some barriers are met. One is set up by the health care system, where complex rules of funding dictates the availability of specialist services (Docherty, 1997). Another is the patient resistance, which may appear as an obstacle in the referring procedure. Patients' beliefs about the helpfulness of different types of providers and treatment influence the choice of provider (Fortney et al., 1998) and many patients have negative attitudes towards psychiatric treatments (Demyttenaere et al., 2000). More than half of primary care patients may be hesitant to see a mental health specialist (Williams et al., 1999). Those who attribute their symptoms to medical illness are especially reluctant to accept a referral (Olfson, 1991b).

4.9.11 Differences in patients with depressive disorders between primary care and specialist care

Due to the many factors influencing on the referring process, the division of patient populations may not be optimal between primary care and specialist mental health care. Only few studies, however, have focused on the actual differences between depressive disorders in primary care vs. mental health specialist care.

Of the large epidemiological surveys, ECA has compared patients with depressive disorders receiving their treatment in the general medical setting to those receiving their treatment in the psychiatric setting. Psychiatric setting was in ECA associated with co-morbidity and history of inpatient care (Cooper-Patrick et al., 1994, Burns et al., 2000).

In the Medical Outcome Study (MOS), mental health specialists, especially psychiatrists, encountered more severely depressed patients, but patients in all sectors were sick enough to warrant treatment (Wells et al., 1995).

Two other major studies with direct comparisons between settings have shown minimal differences in patient characteristics. The first of these included patients with new prescriptions (Simon et al., 2001), the latter compared patient consenting to treatment as a part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study (Gaynes et al., 2005).

Screened MDD patients in both primary care and specialist care have been investigated in only one large clinical study, where primary care patients appeared to have less past treatment for depression, but, surprisingly more lifetime co-morbidity (Schwenk et al., 1996). Compared with specialists' patients primary care patients' functional limitations may be different (Stewart et al., 1993) or slighter (Schwenk et al., 1996). Moreover, the patients receiving treatment for depression exclusively in primary care have more adverse attitudes and beliefs to care than those seen in psychiatric care (Van Voorhees et al., 2003). Concerning sociodemographic variables, based on these studies, depressive primary care patients seem to be older, more often female and less educated than specialists' patients are.

5 AIMS OF THE STUDY

In this study clinical characteristics, co-morbidity course and outcome, and pathways of care were investigated in 137 primary care patients with DSM-IV MDD and subsyndromal depressive disorders.

Specific aims of the study were as follows:

I To obtain a broad view on patients' presenting complaints, severity of depression, Axis I, II and III co-morbidity, and on the retrospective longitudinal course of the depression.

II To examine the prevalence and risk factors for current and lifetime non-fatal suicidal behaviour in primary care patients with clinical depression.

III To describe the differences in terms of severity, co-morbidity, and clinical course of depression, suicidal behaviour, attitudes towards treatment and pathways of care between patients with MDD in primary care vs. secondary level psychiatric outpatient and inpatient care.

IV To assess the prospective course and outcome of depressive disorders and whether features of depression itself and co-morbidity would significantly predict them.

6 MATERIALS AND METHODS

6.1 General Study designs

The Vantaa Primary Care Depression Study (PC-VDS) is a naturalistic and prospective cohort study concerning major and subsyndromal depressive disorders in primary health care. It forms a collaborative depression research project between the Department of Mental Health and Alcohol Research of the National Public Health Institute, Helsinki, Finland and the Primary Health Care Organization of the City of Vantaa, Finland. Vantaa is a city of 179856 inhabitants (in 2002). The catchment area in Vantaa comprises two districts with about 63400 inhabitants, served by 30 general practitioners with population-based responsibility. The western sampling area represents a more affluent, and the eastern a more disadvantaged part of the city; together, these two areas are sociodemographically representative of the whole of Vantaa (2002).

Because of the different foci of the studies, the publications had different patient samples as presented in Table 4.

Table 4. Composition of study populations in the original publications.

Study Number	Vantaa Primary Care Depression Study (major depressive disorders and subsyndromal depressive disorders)	Vantaa Depression Study (major depressive disorders)	Total number of patients
Study I	Patients evaluated at baseline, N=137		137
Study II	Patients evaluated at baseline, N=137		137
Study III	Patients evaluated at baseline, N=74 (46 patients with subsyndromal depressive disorders and patients over 59 years excluded)	Patients evaluated at baseline, N=269	343
Study IV	18-month follow-up, N=134		134

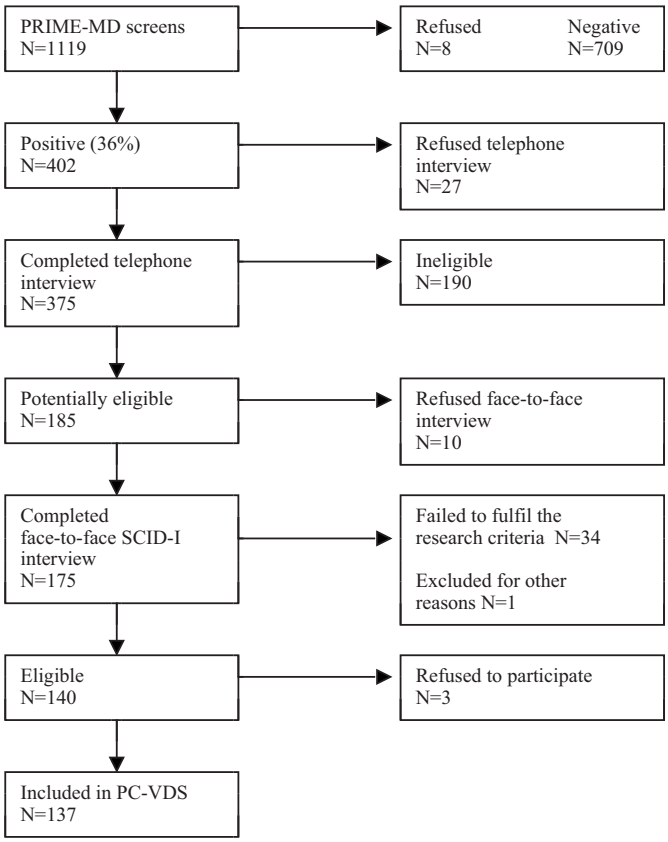
6.2 Screening

Primary Care Evaluation of Mental Disorders (PRIME-MD) (a 27-item self-report screening questionnaire designed to facilitate the diagnosis of common mental disorders in primary care) (Spitzer et al., 1994) was given to consecutive patients, aged 20-69, in general practitioners' waiting rooms on randomly selected days between 2 January and 31 December 2002, stratified in terms of weekday, day of month and time of year in the first stage of the patient sampling. It was not offered to subjects not understanding Finnish (N=50), in medical emergency (N=14) or to handicapped subjects unable to communicate (N=4). Altogether 1119 patients received PRIME-MD. Screening was considered positive if the patients answered "yes" to either question concerning depressed mood or anhedonia in PRIME-MD ("during the past month, have you often been bothered by: (1) feeling down or depressed or hopeless, or (2) little interest or pleasure in doing things"). The 402 screening positive patients were fully informed about the study and were asked for their permission to accept a phone call within five days from the research psychiatrist (M.Vuorilehto).

A total of 375 consenting patients, after PRIME-MD screening, were interviewed by phone by the researcher (MV) for 20-30 minutes. Previous psychiatric diagnosis and current treatment were asked; symptoms of depression were assessed with the current depressive episode module of Structured Clinical Interview for DSM-III-R Axis I Disorders Patient Edition (SCID-I/P) (First et al., 2001). Patients with depressive mood or anhedonia plus distress or impairment due to depression for at least two weeks during the previous month were included. Exclusion criteria were current treatment by a psychiatrist (N=32), bipolar or organic mood disorder, or psychosis other than depressive (N=14), and alcohol use problems severe enough to prevent the diagnostic interview (N=10).

The detailed methodology of the Vantaa Depression Study (VDS) has been reported elsewhere (Melartin et al., 2002). In short, the PC-VDS was planned to be comparable with the VDS. In VDS, in secondary psychiatric out- and inpatient care, patients aged 20-59 years were screened for an incident major depressive episode if they were seeking help by self-referral, referred to treatment, or were already in treatment but had an acute deteriorating clinical state (Melartin et al., 2002). The screening instruments in the VDS comprised the five screening questions for MDD from the Schedules for Clinical Assessment of Neuropsychiatry (SCAN) (Wing et al., 1990) and the Scale for Suicidal Ideation (SSI) (Beck et al., 1979). Exclusion criteria in the VDS included diagnosis of bipolar mood disorder or schizophrenia. Of the 806 patients who were screened, 703 were positive; of them 161 refused further interview (22.9% of the screened).

Figure 5. Flow chart of the screening process in Vantaa Primary Care Depression Study.



6.3 Baseline evaluations

6.3.1 Diagnostic measures

The 175 potentially eligible patients, after giving their written informed consent, were interviewed face-to-face using DSM-IV SCID-I/P with psychotic screen to ascertain whether or not the mood episode during the previous month satisfied the inclusion criteria for the cohort: 1. current MDD, 2. Dysthymia, 3. subsydromal depression (subMDD) with two to four current depression symptoms (at least one core symptom) and fulfilling the criteria of lifetime MDD, or 4. Minor Depression (MinD) with two to four depression symptoms (at least one core symptom) without any history of MDD, thus satisfying DSM-IV criteria. Current distress or functional impairment was required for inclusion in all these groups. Dysthymia was recoded as a co-morbid diagnosis. Four (3%) patients who fulfilled the diagnostic criteria of Dysthymia and had a lifetime history of MDD were included in the subMDD group; one patient without a history of MDD was included in the MinD group.

All available medical records, including the results of a standardized set of laboratory tests, were used to exclude substance-induced depression or depression due to medical conditions. Patients currently abusing alcohol or other substances were interviewed after two to three weeks of abstinence, in order to exclude substance-induced mood disorders. In order to gain a full picture of current (previous month) and lifetime Axis I disorders each patient's inclusion in the study cohort was followed by an interview with use of the entire SCID-I/P with psychotic screen. SCID-II (First et al., 1997) was used to assess diagnoses on Axis II. Axis III diagnoses were evaluated via a self-report questionnaire and information from medical records and the interview. Chronic medical illness diagnosed by a doctor, minimum duration three months and with functional impairment and/or constant suffering, was regarded as current somatic co-morbidity.

The diagnostic joint reliability was analysed by using 20 randomly selected videotaped interviews concerning diagnostics of mood disorders, modified so as not to reveal to the second diagnostician (T.Melartin) the first interviewer's (MV) decisions. The observed agreement rate for current MDD and current subsyndromal diagnoses was 100%, with kappa coefficient=1.0, for both.

In the VDS, current episode of MDD and Axis I co-morbid disorders were diagnosed in a face-to-face interview using the World Health Organization Schedules for Clinical Assessment in Neuropsychiatry, version 2.0 (SCAN) (Wing et al., 1990). The SCID-II for DSM-III-R (Spitzer, 1987) was used to assess the Axis II disorders. Due to differences

between the diagnostic tools only current alcohol dependence was reported among the substance use disorders in the comparison between primary care and psychiatric care. The final study group consisted of 269 psychiatric patients all with a current episode of MDD. Inter-rater agreement in diagnostic interviews was excellent (kappa coefficient=0.86)(Melartin et al., 2002).

6.3.2 Observer and self-report scales

Observer report scales included the 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) , the Scale for Suicidal Ideation (SSI) (Beck et al., 1979) and the Social and Occupational Functioning Assessment Scale for DSM-IV (SOFAS) (Goldman et al., 1992). Self-report scales included the 21-item Beck Depression Inventory (BDI) (Beck et al., 1961), Beck's Anxiety Inventory (BAI) (Beck et al., 1988), the Beck Hopelessness Scale (HS) (Beck et al., 1974) and the Perceived Social Support Scale – Revised (PSSS-R) (Blumenthal et al., 1987).

6.3.3 Other characteristics

A retrospective lifetime course for depression (age of onset, duration and recurrences before entry, as well as chronicity of MDD according to DSM-IV criteria) was reconstructed from the interview and medical and psychiatric records. Age at illness onset was defined as onset of the first mood episode that fulfilled DSM-IV criteria for a MDE.

Patients were asked the subjective reason for their index visit to the primary care doctor. The reasons were classified as: 1. somatic, if the patient reported it as either preventive or only somatic, 2. psychological, if it was only psychological or psychological accompanied by somatic. The specific presenting complaints were asked in a questionnaire, which also included a standard battery of sociodemographic variables (age, gender, marital status, education and employment status).

Suicidal behaviour was investigated in three time frames: a) current suicidal ideation, b) ideation and attempts within the ongoing depressive episode, and c) lifetime ideation and attempts. Here, suicidal ideation refers to patients who scored ≥ 6 on the SSI. Suicidal behaviour during the ongoing depressive episode and lifetime suicidal behaviour, was reconstructed from medical and psychiatric records and by questioning the patient about seriously considered or attempted suicides. By definition, a suicide attempt had to involve at least some degree of intent to die; self-harm with no suicidal intention was not classified as a suicide attempt. The number of visits with the primary care doctor and doctors' notes about suicidal behaviour were calculated from medical records of the preceding year. Consultation with the doctor about depressive symptoms during the current episode was asked about in the interview. Lifetime treatment history for depression and current use of medication was reconstructed from the interview and medical and psychiatric records.

Attitudes towards antidepressant and psychotherapeutic treatments were assessed separately in the interview with the following response alternatives: 1) actively wants treatment, 2) passively accepts treatment, 3) has reservations about treatment, 4) has a clearly negative attitude towards treatment, and 5) could not answer. In the analysis, items 1 and 2 were considered positive attitudes and items 3 and 4 were considered negative (Melartin et al., 2005).

The point of first contact with health care for depressive symptoms was classified as either a) general medical or b) mental health contact. Contacts involving either the patient's active seeking of help or recognition of depression by a healthcare professional were included as first contacts. General medical contact was defined as seeing a non-psychiatric physician or other health professional in any primary care or medical setting (in Finland addiction treatment settings are usually regarded as a part of primary care; 1 primary care patient and 5 psychiatric patients had first contacted there in this study). Mental health contact was defined as either seeing a psychiatrist or psychologist (irrespective of setting) or any other professional (e.g. nurse or social worker) in psychiatric care.

Patients who refused further study participation at any stage (15%) did not differ significantly in age or gender from those who complied.

6.4 Follow-up

6.4.1 Study population in the follow-up

During the 18-month follow-up time the diagnosis of four patients (3%) switched to bipolar disorder; they were censored in the survival analysis at the time-point in the life-chart where the switch occurred. The final follow-up group in the survival analysis consisted of 134 patients, all with information from at least one of the three follow-up points: 89 patients with baseline MDD and 45 with baseline subsyndromal depressive disorder, of the latter, 32 subsyndromal depression with a history of MDD (subMDD) and 13 with baseline MinD.

6.4.2 Study drop outs

Of 137 subjects at baseline, only three subjects (2%) dropped out from all follow-ups. In addition, two more subjects (2%) were missing at 6 months and altogether 10 subjects (7%) at 18 months. Besides them, the four patients with bipolar disorders were not present at the 18-month interview.

6.4.3 Integration of information into a life-chart

Patients were prospectively followed up with a life-chart – similar to the VDS methodology (Melartin et al., 2004) – to determine the duration of the index episode and the timing of possible relapses and recurrences. Information was gathered at three time-points: the BDI was rated at 3, 6 and 18 months, self-report scales were included at 3, 6 and 18 months, and the current diagnosis of depression was investigated by telephone at 6 months and face-to-face at 18 months (median 18.7) by SCID-I interviews. In addition, observer scales were used at the 18-month assessment. To improve the accuracy of the assessment of change points in the psychopathologic states, probes relating to important lifeevents were used. All available data was used, including patient records during the follow-up, which was then integrated into the graphic life-chart. For that purpose, notes concerning the patients' psychopathologic state in the primary care medical records were thoroughly examined; at the same time the number of visits to the primary care doctor were counted. Those contacts with the doctor were counted separately that included according to the notes, discussion about the patients' depressive disorder or its symptoms.

6.4.4 Definitions for time periods of life-chart

The life-chart was based on DSM-IV criteria and definitions. The time after the baseline was divided into periods spent in three kinds of symptom states: (1) state of MDE (5 or more of the 9 MDE criteria symptoms), (2) state of partial remission (1-4 symptoms) or (3) state of full remission (no symptoms).

6.4.5 Principal outcome measures

Besides the cross-sectional diagnostic status at the end of the follow-up period, the principal outcomes for baseline MDD were 1) duration of index MDE with full criteria, 2) time to full remission after index MDE, 3) relapses and recurrences. For the baseline subsyndromal depressive disorders the principal outcome measures were 1) time to the turnover of the subsyndromal symptom state to a MDE, or to non-symptomatic state (Table 5.).

Definitions of remission and relapse followed DSM-IV criteria, and recurrence followed the DSM-IV definition for "296.3x MDD, Recurrent". State of remission (further specified as full or partial) required at least two consecutive months in which MDE criteria were not met. Relapse referred to the return of symptoms fulfilling MDE criteria after a period of more than two weeks but less than two months with symptoms below the MDE threshold. Recurrence referred to the return of MDE after at least two consecutive months of partial or full remission.

Table 5. Definitions of the time after the baseline among patients with depressive disorders in Vantaa Primary Care Depression Study.

Patients with major depressive disorder at baseline	
1) Duration of major depressive episode (MDE) in full criteria (5 or more symptoms)	The uninterrupted duration of the episode in the state of MDE
2) Time to full remission	Time to the first onset of state of full remission (no symptoms) lasting at least two consecutive months
Patients with subsyndromal depression at baseline	
1) Time to non-symptomatic state	Time to the first onset of state of full remission or with no symptoms lasting at least two consecutive months
2) Time to MDE	Time to the first onset of state of MDE with full criteria (5 or more symptoms)

6.5 Statistical methods

Between-group comparisons involving categorical data were computed using the chi-square statistic with Yates' correction for continuity, and Fishers' exact test when appropriate (expected cell count less than 5 in a 2x2 table), while between-group comparisons using continuous data were computed with either Student's t-test, Kruskall-Wallis or Mann-Whitney test, depending on the type of distribution. Multivariate methods, including binary and multinomial logistic regression models, were used to adjust for confounding factors. In the analyses on outcome Kaplan-Meier survival curves were used to estimate the probability of remaining ill during the 18-month follow-up. Cox proportional hazards models were used in the multivariate analyses for predicting time to a change in the symptom state. In hypothesis testing a p-value $<.05$ was considered significant. 95% confidence intervals (95% CI) were used when appropriate. Statistical Package for the Social Sciences for Windows (SPSS) software, version 11.0, 12.0, and 14.0, was used.

7 RESULTS

7.1 Sociodemographic features of the study cohort

The cohort of 137 patients consisted of 76% women, mean age 44.4 years, and 24% men, mean age 48.1 years with no significant sociodemographic gender differences. Of patients 35% were living alone, and 20% were unemployed. Overall, 62% of the patients were recruited from western Vantaa, reflecting the proportions screened in each area and the general population distribution (Study I).

7.2 Current severity of depression and retrospective longitudinal course

Two thirds (66%) of the cohort suffered from current MDD, which was distributed evenly between mild (39/91) and moderate MDD (45/91); a few had severe MDD (7/91). Of current MDD 21% was persistent.

One third (34%) of the cohort suffered from subsyndromal depressive disorder. Of them, only one third (14/46) were true MinD cases. Two thirds (32/46) were subsyndromal patients with lifetime MDD (subMDD), of whom 59% were currently in partial remission, and 41% had already been in full remission prior to current symptoms. The MinD and subMDD patients had significantly less depressive and anxiety symptoms than the MDD patients (HAMD 12.3 [S.D.5.9] vs. 11.9 [4.1] vs. 18.2 [4.7] $p<0.001$, BAI 8.3[S.D.2.8] vs. 9.1 [5.6] vs. 20.9 [13.2]). Of the MDD and the subMDD patients two thirds (77/123) had had at least one and one third (46/123) three or more preceding MDEs (Study I).

7.3 Contacts with health care

7.3.1 Reason for index visit and specific presenting complaints

One third of patients (47/137) reported a psychological reason for the index visit such as "burn out" or "anxiety", which was independently predicted by higher HAMD score (OR 1.15 [95% Cl 1.06-1.24] p=0.001) and younger age (OR 0.97 [0.94-0.99] p=0.018). Gender, psychiatric or chronic somatic co-morbidity, or phase or duration of depression had no influence on the reported reasons.

Of specific presenting complaints the largest group was various pain symptoms, in 26 % of the patients, which associated with co-morbid anxiety disorder after adjusting for age, gender and medical co-morbidity (OR 3.26 [1.27-8.40] p=0.014). Of specific presenting complaints "depression" or "burnout" (21/137) was independently predicted by higher HAMD (OR 1.16 [1.05-1.29] p=0.004) and younger age (OR 0.96 [0.92-0.99] p=0.04) (Study I).

7.3.2 Retrospective contacts with health care among patients with MDD

Of the patients with MDD, 37% had not contacted health care for depressive symptoms during this episode; their depression was markedly milder and fewer of them had positive attitudes towards medication (33% vs. 72%, p=0.001). Half (50%) of the primary care patients with MDD had initially contacted general medical services. The remaining 13%, with more suicidal behaviour during the ongoing episode (50% vs. 16%, p=0.039), had directly approached mental health services.

Of all patients with MDD, 22% had contacted mental health services at some point during the ongoing episode. The majority of these patients had a chronic course (63%) and severe symptoms of depression (HAMD 21.3 [SD 4.56]), with co-morbid personality disorder (75%); during the MDE half of them had considered suicide (50%) and a quarter had attempted it (25%) (Study III).

7.3.3 Contacts with primary care doctor during the follow-up

During the 18-month follow-up, one or more visits to a primary care doctor could be verified from the patient records in nearly all patients (117/123). For patients with baseline MDD the median number of visits was 7 (percentiles 25-75: 4-11), for patients with subsyndromal depressive disorders it was 5 (2-8).

According to notes made by doctors, 81% (64/79) of the patients with MDD had discussed their depression with their primary care doctor; median number of contacts where depression was an issue was 2 (percentiles 25-75: 1-6). Of patients with baseline subsyndromal depressive disorders 59% (26/44) had discussed depression during a median one (0-3) contact (unpublished data).

7.4 Co-morbidity

7.4.1 Current Axis I, II and III co-morbidity

Nearly all patients had current co-morbidity (Figure 6.). In univariate analysis highest rates in overall psychiatric co-morbidity, as well as in anxiety and personality disorders were found in the MDD group (Tables 6. and 7.)

Figure 6. The overlapping co-morbidity in depressive disorders among primary care patients.

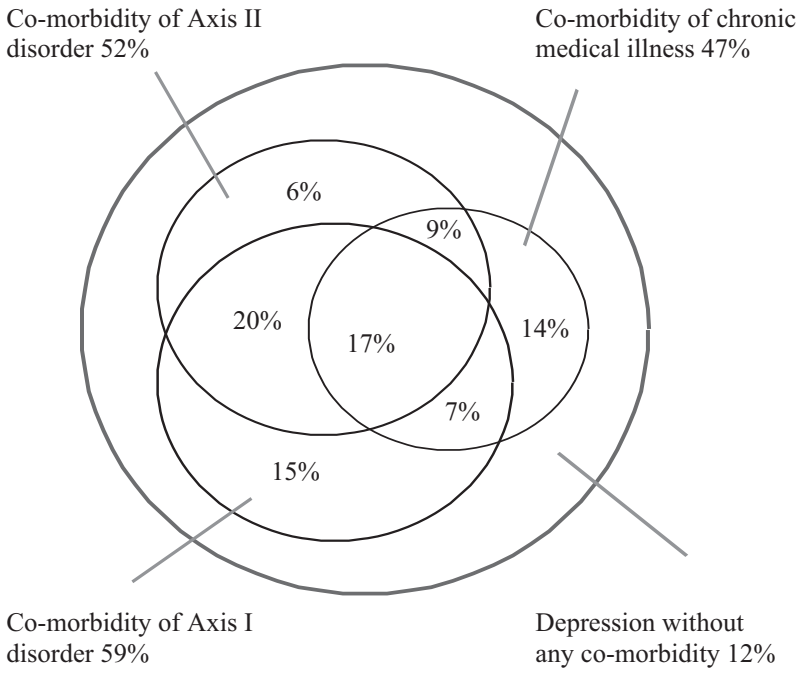


Table 6. Any co-morbidity, medical co-morbidity or Axis I co-morbidity in primary care depressive disorders.

	Major depressive disorder (N=91)	Subsyndromal depressive disorder (N=32)	Minor depression (N=14)	P-value
Any co-morbidity	95 %	81 %	57 %	<0.001
Psychiatric co-morbidity	82 %	66 %	50 %	0.028
Chronic medical co-morbidity	50 %	44 %	27 %	NS
Co-morbid Axis I diagnosis				
Dysthymia	12 %	9 %	7 %	NS
Anxiety disorder	50 %	25 %	36 %	0.036
Eating disorder	2 %	3 %	-	NS
Somatoform disorder	14 %	12 %	-	NS
Substance use disorder	16 %	3 %	7 %	NS

Table 7. Axis II co-morbidity in primary care depressive disorders.

	Major depressive disorder (N=91)	Subsyndromal depression with a history of major depression (N=32)	Minor depression (N=14)	P-value
Co-morbid Axis II diagnosis	58 %	47 %	21 %	0.030
Cluster A	7 %	3 %	-	NS
Paranoid	5 %	3 %	-	NS
Schizoid	-	-	-	
Schizotypal	1 %	-	-	NS
Cluster B	35 %	19 %	7 %	0.037
Antisocial	4 %	-	-	NS
Histrionic	2 %	-	-	NS
Borderline	32 %	16 %	7 %	0.048
Narcissistic	7 %	3 %	-	NS
Cluster C	35 %	31 %	14 %	NS
Obsessive-compulsive	12 %	12 %	7 %	NS
Dependent	3 %	-	-	NS
Avoidant	20 %	22 %	7 %	NS
Passive-aggressive	7 %	3 %	-	NS

After adjusting for HAMD, the MDD group did not differ from subMDD, whereas the MinD group tended to have a lower prevalence of personality disorders (OR 0.72 [95% CI 0.06-1.02] p=0.054). Psychiatric co-morbidity was associated with higher symptom severity of depressive disorder. This was true for overall psychiatric co-morbidity (HAMD mean 16.8 vs. 14.2, p=0.023), as well as among Axis I co-morbidities for both anxiety disorders (HAMD mean 17.4 vs.15.1, p=0.009) and substance use disorders (HAMD mean 19.1 vs. 15.7, p=0.011). Moreover, it was also true for Axis II disorders (HAMD mean 17.0 vs. 15.2, p=0.048). The total number of all co-morbid psychiatric diagnoses correlated with HAMD scores (Spearman r=0.31, p<0.001) (Study I).

7.5 Suicidal behaviour

7.5.1 Current suicidal ideation in SSI

At the time of the interview, 18% of the subjects scored high on the SSI (≥6). Almost all with high SSI were MDD patients (23/137); of them 15 had attempted suicide. Prior psychiatric treatment was the strongest predictor of high SSI after adjustment for gender (OR=19.60 [95% CI 4.05-94.81] p=<0.001), other predictors were younger age (OR=0.92 [0.87-0.97] p=0.001), hopelessness (HS; OR=1.16 [1.03-1.311] p=0.01) and more severe depression (HAMD; OR=1.14 [1.00-1.31] p=0.046). A history of suicide attempts instead of a history of psychiatric care was associated with a high SSI as well when adjusted to the model (OR=9.08 [2.54-32.39] p=0.001) (Study II).

7.5.2 Suicidal behaviour within the ongoing depressive episode

Of all the patients, 24% had experienced suicidal ideation and 4% had attempted suicide during the ongoing episode. Both ideation and attempts clustered with abundant co-morbidity. The suicidal behaviour was independently associated with psychiatric treatment during earlier episodes; other predictors were younger age, severity of depression symptoms and co-morbid personality disorders as shown in table 8. (Study II).

Table 8. Predictors of suicidal behaviour during the ongoing depressive episode.

	No suicidal behaviour (N=104)	Suicidal ideation (N=27)			Suicide attempt (N=6)		
	Odds ratio	Odds ratio	95% confidence interval	P-value	Odds ratio	95% confidence interval	P-value
Age	1.0	0.95	0.91 to 0.99	0.010	1.01	0.93 to 1.09	NS
Gender	1.0	0.98	0.31 to 3.08	NS	*		
Hamilton Depression Rating Scale score without suicidal item	1.0	1.17	1.04 to 1.32	0.008	1.25	1.04 to 1.51	0.020
Personality disorder	1.0	4.12	1.32 to 12.99	0.015	2.23	0.07 to 3.07	NS
Lifetime psychiatric care	1.0	3.85	1.28 to 11.63	0.012	4.88	0.47 to 50.00	NS

* the group consists of only women

7.5.3 Lifetime suicidal behaviour

Within their lifetimes, 37% of the patients had had suicidal ideation and 17% suicide attempts. Lifetime suicidal behaviour was associated with a current MDD diagnosis and severe symptoms of depression, anxiety and hopelessness, personality disorders and psychiatric treatment history. Treatment in psychiatric care some time over lifetime had very strong association with suicide attempts (OR 18.61 [95% CI 3.85-100.00] $p<0.001$) (Study II).

7.5.4 Notes of suicidal ideation and treatment of depression

Only a quarter of current suicidal ideation had been noted (24%) by the doctors in the medical records. The doctors had, however, recognized the depression in all patients with suicide attempts, and in 70% of patients with ideation, and offered antidepressive medication to 83% and 70% respectively. Of the attempters, 83% had received specialized psychiatric care and 67% had been in psychiatric hospital during the current MDE (Study II).

7.6 Differences between patients with MDD in primary care and specialist care

7.6.1 Sociodemographic differences

The primary care patients, the psychiatric outpatients and the inpatients were similar in age, gender, marital status, educational background, employment status and perceived social support as measured with the PSSS-R. The primary care patients were, however, more often on disability pension for medical reasons than the out- and inpatients (7% vs. 1% vs. 2%, p=0.016) (Study III).

7.6.2 Differences in clinical characteristics

Based on HAMD scores the primary care patients and the psychiatric outpatients were equally depressed (17.9 vs. 18.1), but BDI scores were lower in primary care (23.5 vs. 27.5, p=0.004). The inpatients had significantly more severe symptoms of depression than the other two groups (HAMD 24.9, p<0.001) and a lower level of functioning in SOFAS (primary care patients 54.9 vs. outpatients 53.9 vs. inpatients 41.7, p<0.001), and psychotic subtype among them was markedly higher (1% vs. 5% vs. 26%, p<0.001) (Study III).

7.6.3 Differences in Axis I and Axis II co-morbidity

Compared with primary care patients, psychiatric outpatients and inpatients had more agoraphobia (3% vs. 11% vs. 13 %, p 0.049), the inpatients more alcohol dependence (primary care patients 4% vs. outpatients 11% vs. inpatients 30%, p<0.001). On the other hand, somatization disorders were present only in primary care.

Concerning Axis II co-morbidity, of all three patient groups, in primary care the prevalence of cluster B personality disorders (antisocial, histrionic, borderline, narcissistic) was highest (38% vs. 12% vs. 26%, p <0.001) and Cluster A (paranoid, schizoid, and schizotypal) lowest (5% vs. 18% vs. 26%, p 0.007) (Study III).

7.6.4 Differences in suicidal behaviour

In the comparison of primary care patients, outpatients and inpatients suicidal behaviour (both current, during the MDE, and over the lifetime) was most frequent among psychiatric inpatients (ideation 30% vs. 44% vs. 72%, p <0.001) (attempts 18% vs. 28% vs. 63%, p <0.001) (Study III).

7.6.5 Differences in the clinical history

In all three settings, the age at MDD onset was similar, around thirty years. In two thirds of patients in all settings, MDD was recurrent. During the preceding MDEs markedly fewer primary care patients and outpatients had been hospitalized than the current inpatients (14% vs. 6% vs. 26%, p<0.001). Other aspects in the treatment history of earlier episodes were quite similar: one-half had received treatment from any doctor, one-third had received antidepressive medication and more than one-third had received mental specialty treatment.

The duration of the current episode prior to the study interview was significantly longer in primary care (median 6.1 months [25;75 percentiles 1.5;19.0] vs. 3.5 [2.0; 6.0] vs. 2.5 [1.0;5.0], p=0.002). A chronic course of MDD was almost exclusively found in primary care (22% vs. 2% vs. 0%) (Study III).

7.6.6 Characteristics associated with treatment in psychiatric care

In a logistic regression model, where primary care served as reference category, symptom severity measured with HAMD was a strong predictor of inpatient (OR 1.26 [95% Cl 1.14-1.38] p<0.001) but not of outpatient status. However, when BDI was substituted for HAMD in the model, it proved to be a predictor of outpatient care (OR 1.07 [1.02-1.13] p=0.007) but no longer for inpatient care. Suicide attempts (OR 2.62 [1.11-6.16] p=0.028), alcohol dependence (OR 8.36 [1.56-44.28] p=0.013), and cluster A personality disorder associated with treatment in psychiatric care (OR 5.88 [1.76-19.70] p=0.004); cluster B personality disorder by contrast was very strongly associated with primary care (OR 0.08 [0.03-0.20] p=<0.001). Phobic anxiety disorders or patients' attitudes towards treatment did not have independent predictive value (Study III).

7.7 Prospective course and outcome of depressive disorders

7.7.1 Course and outcome of MDE

7.7.1.1. Outcome of index MDE

Of the 79 patients with baseline MDD who were followed up for the entire 18-month period, slightly more than one-third (38%) achieved full remission of the index episode. Another third (37%) achieved partial remission (1-4 residual depressive symptoms), and a quarter (25%) remained with full MDE criteria (Study IV).

7.7.1.2. Duration of index MDE with full criteria

The median duration of MDE with full criteria was 6.00 months (95% CI 4.00-8.00) after entry. In a Cox regression model, longer duration of MDE was predicted by higher severity of depression in baseline HAMD (Table 9.) as well as by baseline co-morbid substance use disorder (Table 9.). Other baseline characteristics, such as perceived social support or ongoing antidepressive medication did not have significant predictive value after adjusting for the severity of depression and therefore they were withdrawn from the final model. (Study IV).

7.7.1.3. Time to full remission after index MDE

In a Cox regression model, only older age and more severe symptoms of depression at baseline predicted longer time to full remission (Table 9.) (Study IV).

7.7.1.4. Relapses and recurrences

Of the patients with baseline MDD, 75% achieved a symptom state below full MDE criteria. Of these patients in one-third (32%), symptoms fulfilling MDE criteria, however, returned: 8% (5/59) relapsed immediately, 27% had a recurrence. In a Cox regression model, longer time to first relapse or recurrence was predicted by milder depressive symptoms and by not having a cluster C personality disorder (obsessive-compulsive, dependent, avoidant, passive-aggressive) at baseline (Table 9.) (Study IV).

Table 9. Clinical predictors for the course and outcome in 18-months of major depressive disorders in primary care patients according to Cox proportional hazard model.

	Hazard Ratio (95% Confidence Interval)	P-value
Duration of the index MDE with full criteria		
Age, years	1.01 (0.99-1.03)	NS
Gender, male	1.43 (0.81-2.50)	NS
Hamilton Depression Rating Scale score	1.11 (1.05-1.19)	0.001
Co-morbid substance use disorder	3.05 (1.31-7.12)	0.010
Time from study inclusion to full remission		
Age, years	1.05 (1.02-1.08)	<0.001
Gender, male	1.59 (0.58-3.70)	NS
Beck Depression Inventory score	1.05 (1.01-1.10)	0.015
Time from remission to first relapse or recurrence		
Age, years	0.98 (0.94-1.02)	NS
Gender, male	0.64 (0.20-2.00)	NS
Beck Depression Inventory score	0.93 (0.88-0.99)	0.022
Personality disorder cluster C	0.37 (0.15-0.91)	0.030

7.7.2 Prospective course and outcome of subsyndromal depressive disorders

7.7.2.1. Outcome of the index subsyndromal symptom state

During the 18-month follow-up the baseline subsyndromal symptom state improved to a non-symptomatic state in about half of the patients (55%). The subsyndromal state remained persistent in one-fifth (20%), and proceeded to MDE in one-quarter of patients (25%) (Study IV).

7.7.2.2. Time to change from subsyndromal symptom state

The median time from entry to a non-symptomatic state was 6.53 months (95% Cl 3.63-9.43). In a Cox regression model, slower improvement was predicted by chronic medical illness (HR 2.79 [95% CI 1.10-7.05] p=0.031). Slower progress to an emerging or recurrent MDE was predicted by baseline diagnosis of MinD (never having suffered from MDD) (HR 15.08 [1.50-151.86] p=0.21) (Study IV).

8 DISCUSSION

8.1 Main findings

The retrospective investigation revealed current MDD in most (66%), and lifetime MDD in nearly all (90%) clinically depressive primary care patients. Two thirds of the "subsyndromal" cases had a history of MDE, although they were currently either in partial remission or a prodromal phase. Recurrences and chronicity were common. The picture of depression was complicated by anxiety (43%) and somatic co-morbidities (47%), and highly prevalent personality disorders (52%). Psychological reasons for the index visit seemed to suggest more severe depression.

Within their lifetimes, one-third (37%) of primary care patients with depressive disorders had seriously considered suicide, and one sixth (17%) had attempted it. Suicidal behaviour clustered almost exclusively in those with moderate to severe major depressive disorder, psychiatric co-morbidity with personality disorders, and a history of psychiatric care. The majority of patients with suicidal behaviour were receiving treatment for their depression, but suicidal ideation had mostly remained unrecognised.

In the comparison of patients with MDD in primary care with those in secondary level psychiatric care, most suicidal or psychotic patients were receiving treatment in psychiatric care, and those with the most severe symptoms and functional limitations were hospitalized. In other clinical aspects, patients with MDD in primary care were very similar to psychiatric outpatients. Mental health contacts earlier in the current MDE were also common among primary care patients with complicated depression.

The prospective investigation with a life-chart methodology verified the chronic and recurrent nature of depression in primary care. Of patients with MDD one-quarter achieved and maintained full remission in 18 months, while another quarter failed to remit at all. The remaining patients suffered either from residual symptoms or from recurrences. Severity of depression was the most robust predictor of recovery, but also presence of co-morbid substance use disorders, chronic medical illness and cluster C personality disorders also contributed to adverse outcome.

8.2 Methods

This is a unique clinical study in assessing the overall clinical picture including co-morbidity of Axis-I, II and III disorders in a cohort of depressive disorders representing the total case load of primary care depression – both recognized and unrecognized. With use of a life-chart method, both retrospective and prospective course could be followed in detail. The investigation on non-fatal suicidal behaviour in primary care patients with depressive disorders was comprehensive. The clinical picture of patients with MDD in primary care was compared with the comparative characteristics in secondary psychiatric care, including for the first time comparison of Axis II co-morbidity.

8.2.1 Representativeness

The cohort was sociodemographically representative of the city of Vantaa. It probably represents Finnish urban and suburban primary health care patient populations well, as the cohort was carefully screened with rare refusals. The generalizeability, however, of our findings to rural or foreign patient populations remains unknown. The study cohort also reflects the true caseload of primary care doctors, as all co-morbid cases and previously undiagnosed patients were included. However, about one third of employed persons use occupational health care services in Finland (Notkola et al., 1992), which may have somewhat enriched unemployed and retired patients in the cohort. In addition, an unknown number of patients exclusively visiting ambulatory services were not included for feasibility reasons; by clinical experience, their psychological problems might be worse.

For the comparison of primary care and secondary psychiatric care patients a large pooled sample of MDD patients (N=343) was obtained, which effectively represents primary care and psychiatric patients in a health district that provides free-of-charge secondary care psychiatric services in community mental health centres. As health care systems, however, can differ widely even within a single country and at the time of study sampling self-referral to secondary care was allowed, the generalizability of our findings are likely to be most relevant to settings in which patients' own choices are important determinants of the eventual treatment provider. Dropouts are unlikely to have biased our outcome findings, as 90% of the cases could be assessed face-to-face at least once after baseline, and for 98% some or all ratings were available.

8.2.2 Screening

Using a screen at intake aimed at providing an accurate picture of the clinical caseload of depressive disorders, both recognized and unrecognized, met by primary care doctors in everyday work. PRIME-MD is known to be a highly sensitive but quite unspecific screening instrument (Brody et al., 1998), and as such revealed one-third of visitors as screeningpositive. The other available questionnaires have not appeared superior to PRIME-MD (Williams et al., 2002). In telephone interviews, we ensured that all clinically significant depressive syndromes were recruited for the face-to-face SCID-interview.

The probability that a depressive patient will appear in a screened prevalence-based cohort is proportional both to the incidence of onsets and to the duration of the depression; therefore, compared with incidence-based studies, cases of long duration are enriched in this cohort (Cohen et al., 1984). Moreover, the patients were not recruited at similar points in the course of their depression, the duration of the episodes in follow-up are not comparable with results of incidence-based studies.

Concerning the comparison between primary care and specialist care the screening procedure of PC-VDS and VDS differed unavoidably. The VDS included patients at the beginning of more intensive treatment, and thus probably in their worst phase of depression. On the other hand, MDD in psychiatric care might already have been somewhat alleviated due to treatment effects. The PC-VDS focused on the cross-sectional load of MDD, thus also comprising cases with a deteriorating or already remitting phase of illness as well as undetected MDDs.

8.2.3 Diagnosis

The strengths of this study include thorough DSM-IV diagnostic investigation with the use of SCID-I/P and -II, and excellent reliability for depressive disorders. The reliability of depressive disorders in follow-up, and co-morbid psychiatric and somatic diagnoses at baseline remains unknown. Personality disorders were diagnosed during depressive syndromes, a fact that may (Stuart et al., 1992, Peselow et al., 1994, Ferro et al., 1998) or may not (Loranger et al., 1991) inflate their true prevalence. In the post hoc analyses, no significant differences were found in the prevalence of personality disorders between those with current MDD vs. subMDD, which contradicts the view that a difference between at least these levels of depressive symptoms would markedly influence personality disorder prevalence.

Axis III diagnoses were evaluated by a specialist in general practice (M.Vuorilehto) via a self-report questionnaire and information from medical records and the interview. Chronic medical illness diagnosed by a doctor, minimum duration three months and with functional impairment and/or constant suffering, was regarded as current somatic co-morbidity.

8.2.4 Life-chart methodology and the definitions of outcome

The outcome of depression was investigated by using a graphic life-chart, identical to the life-chart used in VDS (Melartin et al., 2004) and with many similarities with the Longitudinal Interval Follow-up Evaluation (LIFE) methodology used in NIMH-CDS (Keller et al., 1987). As in the LIFE, change points in the psychopathologic state were assessed using probes related to important events; BDI ratings were used at three time-points and all available patient records. Some degree of underestimation or fluctuation of psychological symptoms, however, may have taken place due to possible recall bias. In this study, patients' follow-up time was classified into periods of DSM-IV MDE, partial remission, and total remission. The major advantage of this classification is that it counts episodes and defines recurrences precisely, as does any clinician when using the DSM-IV.

However, as no universally accepted definitions of remission exist (Keller, 2003), comparison with other studies using similar methodology but with different criteria for remission, should be made with caution. Comparisons with other primary care studies cannot be made, as only cross-sectional outcomes have been reported so far from comparable patient samples.

8.2.5 Limitations of the study

The limitations of the study include moderate final sample size despite a rather large screened patient population. Some subgroups remained small, especially the patients with suicidal behaviour during the ongoing episode, due to the relative infrequency of suicidal behaviour. Nevertheless, the main findings were statistically highly significant and consistent. Concerning clinical history and the follow-up, to avoid recall bias, all possible medical and psychiatric records were used to ensure correctness. Some degree of underestimation or fluctuation of psychological symptoms, however, may have taken place due to possible recall bias.

Concerning research on suicidal behaviour, the cross-sectional nature of the study limits the possibility of making causal inferences. Moreover, when applying the results to suicide prevention, it is to be remembered that this study only concerns non-fatal suicidal behaviour. Despite the largely overlapping of clinical risk factors for suicide attempts and completed suicides, these populations are known to be distinguished by at least age, gender and method (Beautrais, 2001).

In the comparison between primary care and psychiatric settings, the main limitation is the unavoidably different screening procedure of the two studies from which the samples were drawn. The VDS included patients at the beginning of more intensive treatment, and thus probably in their worst phase of depression. On the other hand, MDD in psychiatric care might already have been somewhat alleviated due to treatment effects. The PC-VDS focused on the cross-sectional load of MDD, thus comprising cases with a deteriorating, or

already remitting phase of illness, or stable non-responders to treatment. Possible inclusion of more chronic cases in the PC-VDS has been taken into account in the regression models, which have been adjusted for the duration of the current episode.

Minor differences between the two diagnostic interviews in the comparison, SCAN and SCID-I, could affect the prevalence of single diagnostic groups slightly. Therefore, we included current alcohol dependence instead of total substance use disorders. Also Axis II disorders in the DSM-III-R version compared with the DSM-IV version suggests slightly altered number of items for antisocial and borderline personality disorders, this may increase the prevalence of cluster B disorders in primary care with some percentages (Mantere et al., 2004), but is unlikely to markedly influence the findings.

Concerning the factors associating with the outcome of MDD, those predictors were deliberately focused on those that were present and recognizable to the doctor at intake. Thus all events during follow-up were disregarded that may have influenced the course of depression, including many psychosocial factors together with the complex process of seeking, receiving and complying with treatment. The adequacy of treatment and reasons for the scarce contacts for depression during follow-up is a subject of a further study; as a baseline characteristic, current antidepressant treatment was an insignificant predictor after adjusting for the severity of depression and therefore not included in the final statistical models.

To the extent that other studies have investigated the same characteristics, no major differences between these findings and those from primary care in other countries are apparent.

8.2.6 The severity and long-term course of depressive disorders

The retrospective investigation showed a fluctuating course of depression in primary care, where most depressive patients in fact suffer from MDD, although at the time of contact are possibly in partial remission or a potential prodromal phase. The seemingly cross-sectional "subsyndromal" depressions formed a heterogeneous group. Judd has reported a comparable finding from a survey on the general population (Judd et al., 1997). Furthermore, a large number of recurrences of depressive episodes and chronicity in a fifth of MDD cases was found in this study, similar to the findings of population surveys and studies in psychiatric settings (Solomon et al., 2000, Spijker et al., 2002).

8.2.7 Contacts with health care

Two thirds of depressive patients presented with somatic complaints as in earlier studies (Gerber et al., 1992, Simon et al., 1999b), many of them with pain complaints, which may often discriminate depressed patients from non-depressed (Gerber et al., 1992). No association existed between somatic complaints and chronic somatic co-morbidity. Kroenke has found that a third of primary care patients' somatic symptoms are unexplained and

correlate with anxiety and depression (Kroenke, 2003). In this study, presenting with complaints of anxiety was rare, despite the high prevalence of co-morbid anxiety disorders in the cohort; some somatic complaints may have arisen from somatic manifestations of anxiety. An earlier finding of association between presenting with pain and having co-morbid anxiety disorder was replicated here (Von Korff et al., 1996a).

It is noteworthy that despite the high level of psychiatric co-morbidity and thus multiple concurrent psychiatric syndromes, co-morbid syndromes or symptoms exerted little influence on the presenting complaint. Besides younger age, psychological presenting complaints associated clearly only with higher severity of depression, which may partly explain why milder cases are more often missed (Coyne et al., 1995, Harman et al., 2001, Thompson et al., 2001). Similarly with individuals' seeking of treatment in epidemiological studies (Hämäläinen et al., 2004) primary care patients seem to present with psychological symptoms mostly when their current level of depressive symptoms is distressing.

8.2.8 Co-morbidity

Co-morbidity was more a rule than an exception in this cohort, and only a tenth of patients were free from any co-morbid psychiatric or chronic somatic illnesses. Of Axis I disorders, anxiety (43%) and substance use disorders (12%) were most common. In addition, the proportion of subjects with personality disorders (52%), especially borderline personality (25%), was high. The pattern of co-morbidity was highly heterogeneous, with often either somatic or psychiatric concurrent disorders dominating the clinical picture, and variable in terms of severity and clinical significance. While some single co-morbid disorders barely reached the diagnostic threshold and were of exclusively academic interest, others formed disabling conditions of multiple clustered syndromes, particularly when substance use and cluster B personality disorders were included. Altogether, it appears that there is much more diagnostic heterogeneity and complexity in primary care depression than is usually thought.

Co-morbidity may also have influence on the severity and course of depression. While the number of co-morbid psychiatric illnesses associated with recurrence and chronicity, and both Axis I and II co-morbidities associated strongly with the severity of depressive symptoms – as also in the general population (Kessler et al., 2005b) - chronic somatic illnesses had no influence on depression characteristics.

The prevalence rates of anxiety and personality disorders were higher in this cohort with depression than in the general population (with or without depression) (Bijl et al., 1998, Torgersen et al., 2001), but their presence here was roughly similar to findings in individuals with MDD in population surveys (NCS-R) (Kessler et al., 2005b) and in specialized care (Melartin et al., 2002). This suggests that they either strongly associate with depression or with treatment-seeking from health care, or both.

8.2.9 Suicidal behaviour

Suicidal behaviour clustered in a subgroup of patients with characteristics that had made their depression recognisable such as severe symptoms of depression and personality disorders. Their psychiatric characteristics appeared very similar to both unselected suicide attempters (Hawton et al., 2003) and completed suicides (Foster et al., 1997, Cavanagh et al., 2003, Arsenault-Lapierre et al., 2004). Non-fatal suicidal behaviour in this study associated strongly with prior psychiatric care, either due to preceding attempts or other psychopathology, similar to completed suicides among patients with depression (Simon et al., 1998, Hoyer et al., 2004). The presence of at least one of following risk indicators - personality disorder, prior treatment in psychiatric care, or moderate to severe depression - had 94% sensitivity for any lifetime suicidal behaviour. Personality disorder or prior psychiatric treatment had 100% sensitivity for lifetime suicide attempts in this sample. Although the high risk patients in this sample were already receiving care for their depression, the suicidal ideation itself had mostly remained unnoticed, which is fully convergent with findings from psychological autopsy studies of completed suicides (Isometsä et al., 1995).

8.2.10 Differences between primary care and psychiatric care in MDD

When comparing patients with MDD to those in psychiatric care, some differences between settings seem rational and consistent with the principles suggested in practice guidelines. Psychotic depression was present almost exclusively in the psychiatric hospital. Moreover, the prevalences of suicidal ideation and attempts were highest there, in line with Simon's report of the highest suicide mortality being found in hospitalized MDD patients (Simon et al., 1998, Simon et al., 2001).

The gradient of clinical severity and complexity, reported in general population surveys as a factor that influence the choice of service provider (Hämäläinen et al., 2008), did not associate in this study with professional help in all aspects. Differences in the severity of depression between primary care and psychiatric outpatient care did not exist in HAMD, although BDI scores were higher in psychiatric outpatient care when compared with all patients in primary care with MDD; after excluding unrecognized MDD cases, however, the difference lost significance. Earlier, higher HAMD scores in mental health services were reported in the MOS, which also included milder depressions (Wells et al., 1995). By contrast, comparisons of patients in need of treatment (Gaynes et al., 2005) or beginning antidepressive medication (Simon et al., 2001) revealed no significant differences in severity scores between settings. In complexity, only modest differences were found in terms of Axis I co-morbidities, notwithstanding current alcohol dependence, which formed a strong predictor for inpatient treatment and to a lesser extent for outpatient treatment. This contradicts earlier reported similarities in current substance use disorders between settings (Cooper-Patrick et al., 1994, Burns et al., 2000).

Personality disorders were present in equal number in all settings, but the clusters were unevenly distributed: predominance of cluster A disorder was found in psychiatric care, which might be related to its "odd" appearance. In primary care cluster B disorder, mostly borderline personality disorder, was present in one-third of patients. To some extent, this might relate to the chronicity of depression in primary care. Whether it also reflects reluctance of primary care doctors to refer patients with poor motivation or suspected non-adherence to more intensive treatment remains unknown.

8.2.11 Pathways in treatment among patients with MDD

In this study the patients, according to their pathways in treatment, may be traced in various phases. Firstly, those with no contacts due to depression, representing the second level of pathways to care introduced by Goldberg (Goldberg et al., 1980) made up one-third of primary care MDD with a milder clinical picture, totally in line with many former reports (Schwenk et al., 1996, Hämäläinen et al., 2004).

Thereafter, there are the patients who receive all of their treatment for depression in only primary care (third level by Goldberg), in contrast to those who are later referred to specialist care due to acute need or because treatment in primary care appears insufficient (fourth and fifth level by Goldberg). The final number of patients and their characteristics in these two groups will, besides depending on the recommendations for referrals set forth in the national guidelines, also depend on local cooperation and allocation of responsibilities. In the literature the choice of service provider is likely to be influenced at least, besides patient preference (Fortney et al., 1998), by co-morbidity and severity of depression, suicidal behaviour (ten Have et al., 2004, Hämäläinen et al., 2008), and the availability of services (Fortney et al., 1998).

Finally, the last group in primary care comprises patients without remission of MDD who are returning from specialist care as a consequence of treatment resistance, use of insufficient treatment methods (Alonso et al., 2004b), or perhaps deliberate interruption of treatment by the patients themselves (Melartin et al., 2005). In this study, this group was characterized by rather severe symptoms, co-morbidity and suicidal behaviour. While accounting for a large proportion (22%), this complicated group does not explain all of the severity of depression in primary care. In the research literature the group of patients returning from specialist care, but still suffering from a MDE, is generally overlooked.

8.2.12 Outcome

The prognosis of MDD in primary care was more adverse than in many previous cross-sectional outcome studies (Gaynes et al., 1999, Wagner et al., 2000). As in the earlier studies, large proportions of partial remission (37%) and chronic course (25%) emerged in this study; however, one-third of those with some remission later experienced recurrence or relapse, leaving only one-quarter of patients with a sustained favourable

outcome. Remission also appeared slowly; at six months, only half of the patients had shown some recovery. The duration of MDE has been investigated in primary care earlier only in a cohort of new patients, where the median duration was eight months (Oldehinkel et al., 2000). Overall, our cross-sectional findings were consistent with previous primary care studies, although the life-chart also revealed apparent recurrences and fluctuation of symptoms alongside chronicity. Therefor, this information is fundamental for developing management of depression in primary health care.

The main predictor for poor outcome was higher severity of depression. As in studies in the general population (Spijker et al., 2002) and in psychiatric patients (Keller, 1992, Mueller, 1996, Meyers et al., 2002, Melartin et al., 2004), baseline severity of depression was associated with both chronicity and relapses or recurrences. Moreover, to a lesser extent, co-morbid substance use disorders predicted chronic course of depression; this association has been reported earlier in a univariate analysis in primary care (Barkow et al., 2003). Antidepressive medication at baseline did not associate with outcome in the models that were adjusted for severity of depression. Received treatment may well have influenced the course of depression, but since the course also influences the treatment, and severe symptoms usually associate with more intensive care (Simon et al., 1995), this kind of observational study may end up with no association.

The influence of personality disorders on outcome of depression has previously remained unexamined. Here, cluster C personality disorders appeared to predict early recurrences. Previously, a general population survey (Johnson et al., 2005) reported a similar association, while in specialist care, cluster C personality disorders have mainly been associated with longer duration of MDE (Viinamäki et al., 2002, Farabaugh et al., 2005). Finally, chronic medical illnesses, a known predictor for adverse cross-sectional outcome in both adult and elderly patient groups (Wagner et al., 2000, van den Brink et al., 2002), also formed a risk factor for slow recovery from subsyndromal depression in this cohort.

Concerning subsyndromal depressive disorders the significance of lifetime history of MDD for expected outcome was revealed. While "proper" MinD seldom proceeded to MDE, a new MDE was seen in one-third of those who were in partial remission or in a potential prodromal phase of lifetime MDD. Overall, however, as in the few existing cross-sectional studies (Ormel et al., 1993, Wagner et al., 2000, Lyness et al., 2002), the group with subsyndromal depressive disorders had a better prognosis. As they at entry already had fewer co-morbid psychiatric disorders, they may represent a group in a clinical subgroup of patients more likely to recover.

9 CONCLUSIONS AND IMPLICATIONS

9.1 Conclusions

This study provides a unique clinical picture of the total caseload of primary care depression – both recognized and unrecognized. A broad spectrum of co-morbidity and other clinical characteristics has been assessed, as well as both retrospective and detailed prospective course. Exceptionally, comparison of comparable characteristics of primary care patients with MDD and patients in secondary psychiatric care in the same catchement area has also been possible.

From a lifetime perspective, the majority of primary care patients with depressive disorders suffer from recurrent MDD, and most of the subsyndromal cases represent in fact either prodromal or residual phase of MDD. In prospective investigation, fluctuating course, with high rates of recurrence and chronicity could be verified.

The majority of primary care depression is mild or moderate MDD and complicated by highly prevalent psychiatric and somatic co-morbidity. The cross-sectional caseload of depression consists of a remarkable minority of chronic patients. The clinical picture of MDD is very similar to that in psychiatric outpatient care whereas patients with severe, psychotic and suicidal depression were clustered in psychiatric inpatient care.

Severity of depressive symptoms and co-morbidity are also important predictors for prognosis in primary care. Together with treatment history in psychiatric care, severe MDD and co-morbid personality disorder clusters with suicidal behaviour. Moreover, severity of depression serves well as a predictor of outcome.

9.2 Clinical and research implications

Treatment of depression in primary care cannot rest on an assumption of short-lived, uncomplicated mild disorders. The direction of clinical implications from the longitudinal findings is clear: in clinical decision-making, a history of previous MDD should not be ignored by primary care doctors while depression is usually severe enough to indicate at least follow-up, and concerning those with residual symptoms, also evaluation of their current treatment in order to avoid the high risk of later relapse. Questioning about prior treated episodes, as a clue for clinically significant depression, should be expanded to gathering information on all prior depressive symptoms in order to obtain a

full picture of the course of depression. Severity of depression serves well as a predictor of outcome; primary care doctors in everyday practice should consider this.

Moreover, recognition of suicidal behaviour among depressed patients should also be improved. The complex psychopathology of suicidal depressed patients in primary care needs to be considered in targeting preventive efforts; standard antidepressant therapy in primary care is only a partial solution. Effective treatments that take into account the complex psychopathology need to be developed and evaluated, but what treatment and what kind of cooperation between settings would best benefit them, remains uncertain.

In order to improve outcome of depression in primary care, the often chronic and recurrent nature of depression should be taken into account. Because of the high number of recurrent cases in primary care, long-term maintenance treatment there is often warranted. The findings of this study also support the need of other than acute treatment of depression.

A challenging focus of future research on primary care depression is the management of care, both in communal health centres and in occupational health care. Best ways of allocating resources between treatment providers should be found, as well as the optimal ways of dividing the responsibilities between various kinds of primary care workers and specialists; an integrative view should be reached. Additionally, the ways in which depression care could be integrated into the treatment of medically ill patients is a challenge and an option scarcely used in primary care. Finally, a significant minority with multiple co-morbidity, chronic course of depression and already unsuccessful treatment trials in specialist care is a group needing further examination with the possible development of special treatment programs.

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